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ANNALS OF
INTERNAL MEDICINE

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THE PROBLEM OF THE NEUROTIC PATIENT *

By WILLIAM C. MENNINGER, M.D., F.A.C.P., *Topeka, Kansas*

THE title of my paper, "The Problem of the Neurotic Patient," does not make clear whether the patient or the doctor has a problem. Actually they both have: to the patient his neurotic illness is a problem, to the doctor the diagnosis and treatment of that illness are often a problem.

As a psychiatrist, I represent a minority of the medical practitioners. However, the subject of my discussion, "the neurotic patient," represents a majority of all of the patients who seek help from physicians. This fact is not new but military experience gave dramatic evidence to support it. The discharges with neuropsychiatric diagnoses alone accounted for more than the total of those given for infections, disorders of the gastrointestinal, cardiovascular, respiratory and genito-urinary systems, for ear, eye, nose and throat afflictions, tuberculosis and venereal disease. Considerably more than half of the neuropsychiatric discharges were for psychoneuroses and undoubtedly many neurotic soldiers were discharged under other diagnoses. For every man medically discharged, there is statistical evidence that at least five other men were seen by a psychiatrist for some type of personality disorder which did not lead to discharge. In addition, 150,000 soldiers were discharged through administrative rather than medical channels because of personality difficulties.

This information can be interpreted variously and each interpretation will include some part of the total explanation. It surely reflects the fact that Army life was difficult and exacting and that our way of living had not prepared many American youths for such demands. It probably indicates a critical state of affairs in the American family. It might be construed as evidence of some kind of inadequacy in our system of practicing medicine, and, therefore, as a failure in our medical education. Certainly, it was a disturbing indication of the extent of temporary or existing mental ill health.

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The picture we saw in the Army must exist in modified form in civilian life, since our soldiers were primarily civilians. In any event it presents a major challenge to American medicine upon which the health, both mental and physical, of our people depends.

Most doctors will agree that a high percentage of their patients present emotional problems which either cause or complicate a clinical picture. The family physician of yesteryear who came to the home to see his patient also saw the family relationships as he lingered for a chat over a cup of coffee. He heard about daughter's love affair and son's job, mother's over-work and father's worry. Along with sugar pills, his interest and advice were part of the treatment rendered. Now a doctor sees the patient in the more formal atmosphere of an office or in the hospital. Scientific data have accumulated to such an extent that no one physician can keep abreast of the new technics and skills essential for a "general practice." Consequently, some of us concentrate on trying to be expert in a part of the total field. In such a highly specialized profession we lose contact with each other. We often do not have time or take time to "just listen" to the patient and then evaluate the rôle of the emotional factors in his illness.

Research and experience, while contributing to our knowledge of the reaction of organs and bacteria to new forms of therapy, have also led to greater understanding of the management and prevention of mental illness. Of particular importance is the increasing appreciation of the presence of an emotional factor in all illness. Physicians are looking more and more for knowledge of ways and means to neutralize the emotional provocation of organ dysfunction. Psychiatrists are eager to contribute to other doctors, information gleaned from their study of the seriously disintegrated personality as to what factors help maintain emotional balance and what interfere with it.

We have learned that frequently the patients with prodromal symptoms of serious mental illness are seen first by the laryngologist, the orthopedist, the endocrinologist or the internist. Too often, only when the symptoms become psychologically incapacitating are they brought to the attention of the psychiatrist. Only then is their neurotic reaction diagnosed primarily as such. In many such cases the first doctor consulted by the patients might have aborted or relieved the symptoms. In many other cases earlier referral might have given a better outlook in treatment.

Since neurotic reactions are so complicated, it is neither practical nor pertinent here to attempt a review of their classification nor the details of their pathology. The many positive or negative points about their treatment are necessarily based on the pathology. Consequently these cannot be condensed in this brief presentation even if that were desirable.

Our understanding of that form of emotional illnesses—"the neurosis"—has increased greatly during the last 20 years. But much of this information has not become common knowledge either to our physicians or to our

medical students. Some of us in the Army were impressed repeatedly with the fact that a majority of physicians lacked a working understanding of this large area of medicine. We can lay the blame of this ignorance on improper medical education, on our over-emphasis on mechanical and chemical diagnostic aids, on the intangible quality of emotions or on our still incomplete knowledge of psychiatry. However, to place the blame helps little unless it leads to the correction of our inadequacy. Perhaps touching briefly on some of the deficiencies observed in the Army may be helpful.

Many physicians are quite unable to give any scientific explanation for an hysterical paralysis, a phobia of tuberculosis, or of a so-called organ neurosis. They know that the action of the heart or lungs is involuntary but they have difficulty in recognizing and accepting as valid the fact that a major portion of the personality is not under voluntary control. They have not learned to feel at home with a knowledge of the structure and the function of the personality which includes the basic concept of the existence of an unconscious. Just as jaundice is described in reference to the anatomy and physiology of the liver, a neurotic symptom can be explained only in terms of the anatomy and physiology of the personality.

The psychiatrist considers the unconscious as a major area of the personality function. We make no attempt to structuralize or to locate it anatomically. It is the source of one's life energy, instincts and primitive drives. The unconscious contains at birth the psychological heritage of the organism which is characteristic of his species. It stores the accretions of the individual's development—the forgotten experiences and memories and all of the urges to forbidden activities and desires which are repressed because of parental influence, training, experience, social demands and culture.

From birth through the first years of life the growing child develops a conscious personality through which he maintains contact with his environment. It is a function of this consciousness to attempt to control the primitive energy and instincts which the infant brought into the world with him. As he becomes a mature individual, he learns that society demands that he censor and direct the superior power and drives of the unconscious. To the conscious portion of the personality belongs the responsibility for seeing that the expressions from the unconscious conform to socially acceptable standards and approval.

The mentally healthy personality is able to control the unconscious drives for expression. Nevertheless, even in the well integrated person, their pressure to find an outlet may temporarily overcome all modifications of or defenses against their expression—perhaps in sleep, under the influence of alcohol, as a result of fatigue, in the course of a fever. Or the unconscious drives may gain more permanent expression in the disguised forms which we label neurotic symptoms.

Usually the first indication that the conscious personality cannot control the threatened escape of a primitive impulse or urge is a feeling of anxiety.

This anxiety or uneasiness is a danger signal of an impending threat to self-control. Just as in all biologic phenomena, the organism tries to heal itself. In the case of anxiety, the personality mobilizes its resources to prevent the escape of the impulse. The apprehensiveness, restlessness or fearfulness which are expressions of a conflict between unconscious pressure and conscious control can be resolved sometimes by changes in the environmental situation. Sometimes the conflict can be resolved if the individual gains a better understanding of the factors in his situation to which he is reacting. If the conflict is not resolved, the personality is forced to utilize some type of automatic defense, of which there are many forms.

One defense is to channel the initial impulse into symptom expression—some disturbance of gastrointestinal or cardiovascular function, curiously distorted fears, bizarre compulsive behavior, affections of motor or sensory or visceral functions, or any other so-called "neurotic" symptom. These represent a socially approved escape for the disapproved impulse. What is very important to understand is that the individual himself is no more capable of voluntary control of such symptom formation than of the rate of his heart beat. Such symptoms represent the basic energy drives and appear as involuntarily and as automatically as do one's changes in peristaltic action. Since the initial impulse was unconscious the patient cannot explain its expression. At best he can offer only a superficial rationalization which he himself may regard as inadequate. These are neurotic symptoms.

Each symptom, because it represents a kind of triumph of the powerful unconscious over the conscious control, is a distorted form of gratification. Simultaneously, however, these symptoms are painful and thus they serve as a punishment inflicted by one part of the personality upon another part of it for permitting the escape of a forbidden impulse.

This complicated phenomenon is far too simplified in the above explanation. At times everyone manifests such neurotic symptoms. They do not represent ill health any more than does the minor impairment of any other biological system. Many individuals, although they remain productive and creative, exist continuously only at a level of neurotic adjustment. In other words, the struggle within them is never resolved. Their defenses which are mobilized against the release of the denied impulse, are conspicuous. They show eccentricities or strange mannerisms, curious personal habits or unusual forms of behavior. Strange philosophies or a long suffering wife or husband give them unseen supports in the struggle between their personalities and the world in which they live. When their routine is not grossly disturbed, they are not incapacitated.

When the defenses break down sufficiently so that neurotic symptoms cause incapacity, a diagnosis of some type of neurotic reaction is justified. Sometimes this may be an acute decompensation such as occurred during the war in combat in previously well integrated individuals. It occurs too, not infrequently, in civilians who are under acute emotional stress. On the

other hand, there is the slow cumulative decompensation seen most clearly in the chronic neurotic invalid.

Neurotic reactions are not so simple, however, as to be merely the partial or distorted escape of a primitive impulse from the control of the conscious. The personality is far more complicated. It includes all that the organism starts with—the germ plasm of a given inheritance—plus all of the experiences of his life. In most, if not in all neurotic reactions, a major etiologic factor will be found in a disturbance in the development of the personality.

In both acute and gradual decompensation, severe neurotic symptoms are traceable to psychological injury during infancy and early childhood. Patterns of relationship to the environment, and more particularly to the people in that environment, are established during early life. Then the organism is particularly sensitive, and therefore vulnerable, to traumatic events. The personality of every adult bears some scars of emotional injuries in childhood. Close psychiatric scrutiny will reveal the evidence of drouths, blights, floods and sunny weather experienced by a personality during its development. A deeper scar, resulting from a particularly traumatic event, represents a specially weak spot—an Achilles heel—which is more subject to later damage by an experience in adulthood similar to the one which caused the childhood scar. Under ordinary life situations, such weaknesses are not apparent either to the individual or to the observer.

We see wide variations in the type and degree of reactions of different individuals to the same situation. This fact is apparently confusing to many physicians. They recognize very well that a typhoid inoculation may produce a violent reaction in one individual and no reaction in another. Consequently, it should not be surprising that a particular emotional experience may produce an extremely neurotic reaction in one person but not in another. However, this phenomenon is often interpreted as being faked by the first person, on the basis that it did not produce the same reaction in a second person. It is not easy to explain the varying responses either to the typhoid inoculation or to the emotional stress but both are valid, scientific observations. As a matter of fact, it is probably easier to explain the emotional response than the typhoid response.

Too many doctors also seem unable to accept the validity of a neurotic illness, perhaps because of the scotoma for this field in their medical education. Since they have been taught that illness is physical, a neurotic illness is a paradox because there may be no physical findings, or the physical findings obviously do not explain the complaints. Lacking psychiatric orientation, these physicians have no basis for understanding the phenomena they see. They use the mechanical and chemical diagnostic aids with which they are familiar—the laboratory, the roentgen-ray, the electrocardiograph. In the absence of positive findings, they repeat the examination or search for another source of trouble. They may conclude that the problem is psychological but withdraw in the face of ignorance of suitable treatment methods.

They were taught how to give drugs and prescribe diets but very few medical students—or doctors—have received either formal or informal instruction in the most important therapeutic tool in all medicine—psychotherapy.

The intangibleness of psychopathology in contrast to the visual evidence of physical pathology creates a kind of anxiety in some physicians. One of his responses is seen in the over-examination of a neurotic patient. If this process were harmless, there might be less reason for concern. Instead, as a rule, it intensifies and tends to fix the neurosis. The findings of an examination are impressive to the patient, especially if explained by the physician with an air of great seriousness. Even a minor physical finding can be used by the patient to justify his illness as a "real" (physical) one and enable him to escape the recognition that it is psychological. It should become axiomatic that one cannot compensate for a lack of understanding by making repeated physical or chemical examinations. The technic of making a diagnosis by elimination is rarely justified.

There are many approaches to the examination of the personality. Just as a physician does not merely accept the word of his patient that he has kidney disease, neither should he accept at face value the patient's statement that he has a psychoneurosis. The physician is, or should be, curious as to why the patient thinks he has a particular symptom. He must go further and look for pathology within the troublesome body system. One step preliminary to making a diagnosis of disease of the kidney is an examination of its product. Before mental illness can be diagnosed an investigation of the expressions of the mind and emotions is essential. Just as analysis of the urine may reveal the presence of pathology, an analysis of the emotional products of the mind, e.g., hostility, is an essential examination to reveal pathology of the personality.

The present day physician's attitude toward and understanding of most mental excretions is at about the same point as was the attitude of the medical profession to urine analysis 100 years ago. At that time a few curious physicians looked at it; a very few more brave ones tasted it.

Currently physicians rarely inquire about hate or resentment unless the patient forces this on their attention. Even then they are prone to regard these as unrelated to his heart complaint. Just as physicians have learned that the excretion, urine, is a very important lead to pathology, they will learn to recognize hostility as another kind of an excretion that usually indicates gross pathology. For instance, deep resentment or hatred towards some close associate is always indicative of serious conflicts within the individual's psychological life and may be reflected in many varied symptoms. The presence of strong hostilities should lead to certain diagnostic tests of the personality. These, in turn, would need to be correlated with a study of the psychological metabolism: an evaluation of the intake, the deficiencies or excesses of all the major interpersonal relationships in the individual's life, his loves and his hates and their variations. Medicine has given lip

service, without real conviction, to the idea that we physicians should treat the patient "as a whole," to "comprehensive medicine," or that we should treat the person and not his disease. The fact is that a considerable portion of American physicians still are treating just the disease.

The neurotic patient cannot cure himself. Too often, however, the physician's own personal observation is that there is really nothing wrong with him. In fact, we saw thousands of instances in the Army where the physician so told the patient, though in private practice he is not as likely to do so. Many physicians, however, not knowing what else to do, resort to giving placeboes or platitudes. Neurotic patients can help themselves in their recovery, but only after the doctor has stepped into their environment and helped them reëstablish their equilibrium. He does this by helping the patient reorient himself, both to his internal psychological conflicts and the external environment. Sometimes he must aid in manipulation of that environment. The necessity to have the assistance of a second party, the physician, is due to the fact that the neurotic patient's difficulty is beyond his own control. He needs the help of someone in whom he has faith and confidence, who understands him, who will be patient with him and who will explain him to himself. Only then can he have the courage or the will power to examine his own psychology and thus aid in his own improvement.

The neurotic patient is indeed a very real problem to the average doctor. He presents a special challenge to medicine which for so long has failed to aid him. Our tempo of life with its increasing stresses and strains may be expected to produce even more neurotic symptoms in apparently well people. At the same time, the war's toll in psychoneurotic casualties has increased the awareness of both physicians and laymen of the emotional factors in all disease.

One cannot now help but sense the pulse of increased public interest in mental illness as it has been recently catered to by innumerable articles in national magazines about the neuroses or psychosomatic medicine or psychoanalysis or psychiatry.

This newly awakened interest is a challenge to all medical men. Our Army experience leaves no doubt whatever that the existence of emotional problems in the daily lives of many people is the stimulus for so many feature articles in magazines. It becomes a joint responsibility of all medicine, since certainly 90 per cent of such cases must be handled by the physician to whom the patient goes first, whether he is a general practitioner or a specialist. To prepare himself to handle the problem well, however, the average doctor must take the initiative to acquire the basic facts about the anatomy and physiology and pathology of the personality.

STREPTOMYCIN IN THE TREATMENT OF MENINGITIS: REPORT OF 27 CASES TREATED AT THE BOSTON CITY HOSPITAL *

By Tom Fite Paine,† Roderick Murray, Albert O. Seeler and Maxwell Finland, F.A.C.P., *Boston, Massachusetts*

Cases of meningitis due to *Mycobacterium tuberculosis* or to gram-negative bacilli are not particularly frequent. They are nevertheless of great importance because of their high mortality and their failure to respond to the various types of therapy, including sulfonamides and penicillin, which have given favorable results in the coccal infections. Only a few reports are as yet available on the results of streptomycin therapy in these types of cases. These reports will be summarized briefly and the results in 24 cases of meningitis due to gram-negative bacilli and in three cases of tuberculous meningitis, that were treated at the Boston City Hospital ‡ will be presented in this paper.

The incidence of meningitis due to various gram-negative bacilli and to the tubercle bacillus as given by various authors is shown in table 1. Such cases occur more frequently in children than in adults. Of the gram-negative bacilli, *Hemophilus influenzae* is the one which causes meningitis most frequently. The results in cases due to this organism will be considered first.

Meningitis Due to *Hemophilus influenzae*

This condition occurs largely in infants and small children, particularly during the first two years of life. Strains of *H. influenzae* are of two main varieties: one a smooth, encapsulated and presumably virulent form and the other a rough non-encapsulated and avirulent form. The rough or so-called "respiratory" strains are occasionally implicated as the cause of meningitis, but they usually are found as normal saprophytic inhabitants of the upper respiratory tract of man. The smooth, encapsulated variety, on the other hand, is found mostly in cases of meningitis. In addition to its presence in meningitis, the latter may be found in the respiratory tract usually in conjunction with acute respiratory infections.[13, 14, 15] During respiratory infections the rough form may undergo transformation to the smooth variety.[16] There are six known serological types among the smooth strains of *H. in-*

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From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston, Massachusetts.
With the technical assistance of Clare Wilcox.
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† Research Fellow, American College of Physicians.
‡ The patients were under the care of the resident and attending staffs of several different services. The authors are indebted to them all for their interest and coöperation.

TABLE I

Incidence of Meningitis Due to Gram-Negative Bacilli and *Mycobacterium tuberculosis*

Authors	Cases of Meningitis	Organisms			
		Hemophilus influenzae	Coliform Organisms	Other Gram-Negative Bacilli*	*Mycobacterium tuberculosis*
All Ages					
Neal (1935)[1]	3178	142	8	11	986
Tripoli (1936)[2]	468	20		4	51
Rhoads et al. (1940)[3]	459	29			158
Ferguson and Barr (1944)[4]	72	2	1		6
Rhoads (1947)[5]	550	15	2		16
Brainerd and Bradley (1947)[6]	265	7	5		14
Total	4992	215 (4.3%)	16 (0.32%)	15 (0.30%)	1231 (24.7%)
Infants and Children					
Fothergill and Sweet (1933)[7]	705	78	9	1	290
Lindsay et al. (1940)[8]	642	100		2	205
Silverthorne (1943)[9]	1100	153			368
Neal (1935)[1] (under 3 years)	1077	92	6	4	440
Total	3524	423 (12.0%)	15 (0.43%)	7 (0.20%)	1303 (37.0%)
Autopsies					
Keefer (1941)[10]	83	9			9
Hertzog (1945)[11]	377 (149)†	43 (39)†	10 (9)†	1	56 (16)†
Pote and Courville‡ (1945)[12]	100‡	7§	4§	2	2
		2			
Total	560	59 (10.5%)	14 (2.50%)	3 (0.41%)	67 (12.0%)

* Includes *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, typhoid-dysentery organisms, *Proteus morgani* and others.

† Number of cases under 3 years old.

‡ Meningitis complicating disease of the nose, accessory nasal sinuses or ears.

§ Certain of these were mixed infections, including one case with *Aerobacter aerogenes* and a streptococcus.

fluenzae.[17-20] The type b strains account for over 90 per cent of cases of influenzal meningitis.[20, 21]

The predominance of the disease during the first two years of life may be related to the low bactericidal action of infants' blood against *H. influenzae*, type b, as shown by Fothergill and Wright.[22] The common history in these patients is that of an upper respiratory infection followed by the onset of meningitis. It is assumed that in most cases the organisms reach the meninges by the blood stream following invasion through the respiratory tract. Although *H. influenzae* meningitis is usually a "primary" disease of the meninges, cases of infection may certainly occur by extension from foci of infection in the nasal accessory sinuses and ears or may follow fractures involving these areas.[12, 23]

The use of combined sulfonamide and type specific rabbit antiserum in the treatment of meningitis due to *H. influenzae* type b has resulted in a marked lowering of the over-all mortality rate, from nearly 100 per cent to

as low as 7 per cent.[24] The latter figure, however, is based on the results obtained in one series of 28 cases and other authors have reported higher mortality rates up to 50 per cent, with this therapeutic regime.[8, 25-28] Among the drawbacks to serum therapy in this disease are: (1) Type b antiserum, the only type available, is ineffective if the causative organism is not of this type. (2) The incidence of serum reactions is high; they occurred in 12 of one group of 27 patients and there were two instances of severe anaphylactic reaction in that small series.[24] (3) The cost is high and the antiserum is not generally available.

Penicillin has usually been considered ineffective against *H. influenzae* and it was first used as an aid in the isolation of that organism.[29] It has, therefore, not been given an adequate therapeutic trial in cases of meningitis due to this organism. A number of strains of *H. influenzae* isolated from cases of human infection have been tested for sensitivity to penicillin and the majority of smooth strains were found to be completely inhibited by 1.5 units per ml. or less.[30, 31] Rough strains, however, usually required 2.5 to 5.0 units of penicillin per ml. for complete inhibition and some were not inhibited by 5.0 units per ml.[31] Penicillin X is somewhat more effective than penicillin G.[30] Zinnemann [32] treated 15 cases of *H. influenzae* meningitis with combined sulfonamide and penicillin therapy and eight of these patients recovered. Antiserum was used in only one of these cases and that patient died. The course of the illness in these cases was protracted and relapses were frequent after the therapy was stopped. Others have reported cures from the use of sulfonamides and penicillin in a few cases.[33-37]

Drysdale et al.[38] reported the case of a 20-month old infant who was treated for nine days with sulfonamides and penicillin intramuscularly and intrathecally and cultures of the cerebrospinal fluid remained positive for *H. influenzae* type b. At this point the sulfonamides were discontinued and thereafter penicillin alone was given for about one month. The dosage of penicillin was increased from 100,000 to 500,000 units daily by intramuscular injection and the daily intrathecal dose was increased from 25,000 to 50,000 units for a few days and later changed back to 25,000 units. Cultures of the cerebrospinal fluid were negative after the seventh day on this penicillin dosage. The organism in this case was completely inhibited by 0.7 unit of penicillin per ml., and was found to be insensitive to six different sulfonamides. The penicillin concentration in the cerebrospinal fluid 24 hours after an intrathecal injection of 50,000 units of penicillin and while the patient was receiving 500,000 units intramuscularly daily ranged from 1 to 2 units per ml. However, with the same intramuscular dose of penicillin and 24 hours after the intrathecal injection of 25,000 units of penicillin, the concentration in the cerebrospinal fluid varied from 0 to 1.5 units per ml., with an average level of 0.6 unit per ml. which was less than the minimum inhibiting (complete) concentration of penicillin for this particular organism. Accordingly these authors advise doses of at least 50,000 units of penicillin intrathecally daily in cases of influenzal meningitis.

Inasmuch as certain conditions may arise in the treatment of meningitis due to *H. influenzae* which necessitate a change of therapy the possible usefulness of penicillin should be borne in mind.

Streptomycin is effective against *H. influenzae* in vitro and in experimental infections.[30, 39] The sensitivity of most strains ranges from 1 to 5 units per ml.,[40] concentrations that are easily obtained with therapeutic doses in man.

A number of authors have reported on the effectiveness of streptomycin in cases of meningitis due to *H. influenzae*.[41-52] Among the 100 cases cited in the report of the National Research Council[53] there were 17 deaths. These cases cannot be considered as adequately reflecting the value of streptomycin since other agents were also used in a large proportion of them and the streptomycin was often used only after the other therapies had failed.

On the basis of published reports, the chief hazards of streptomycin treatment in *H. influenzae* meningitis are: (1) the development or appearance of streptomycin resistant strains of *H. influenzae* during treatment and (2) the occurrence of complicating secondary infections due to streptomycin insensitive organisms.

Streptomycin resistant strains of *H. influenzae* have been noted to appear during therapy in five of the patients with meningitis that have been reported to date.[42, 46, 49, 52] These cases are of special importance and some of the details are of interest.

One of the patients reported by Alexander et al.[49] was given a single initial intrathecal injection of 25,000 units of streptomycin and none was given by this route again until the fourth day of treatment. At this time a streptomycin resistant strain of *H. influenzae* was present in the cerebrospinal fluid despite the fact that intramuscular streptomycin had been administered throughout the period. The streptomycin was begun early in the disease in this case. In another patient who developed a streptomycin-resistant strain of *H. influenzae* during therapy the disease had been present for a period of two weeks or longer before the streptomycin was started.[49]

In the patient reported by Birmingham et al.[42] therapy with streptomycin was begun late,—on the eighth or ninth day of disease. Following the daily administration of 240,000 units intramuscularly and 20,000 units intrathecally there was some improvement clinically. After the second day, however, the course was downward, cultures of the cerebrospinal fluid yielded a resistant organism and the infant died despite the additional use of antiserum and sulfadiazine.

In the case reported by Morgan and Hunt[46] a streptomycin resistant strain of *H. influenzae* appeared during therapy of a child who already had cerebral abscesses as well as meningitis when treatment was started.

It should be noted that resistant organisms appeared in three patients in whom streptomycin was begun late in the course of the disease and in a fourth case in which treatment was begun early, but the intrathecal injections were interrupted.

Alexander[52, 54] has reported the appearance of a streptomycin resistant strain of *H. influenzae* type b in the nasopharynx as well as in the cerebro-

TABLE II

Relevant Findings in Cases of Meningitis Due to *Hemophilus influenzae* Treated with Streptomycin at the Boston City Hospital

Case	Age	Previous Therapy	Streptomycin Therapy					Other Therapy	Blood Culture Before Streptomycin	Days from First Dose until C.S.F. Cultures Were All Negative	*H. influenzae*		C.S.F. Levels, Units per Ml.	Outcome	Secondary Fever Attributable to Streptomycin	Remarks on Clinical Course
			Day Begun	Intramuscular		Intrathecal					Type	M.I.C.				
				Mg. per Day	Days	Mg. per Day	Days									
1	4 mos.	Penicillin + sulfadiazine, 1 day	4	500	8	50	6	None	Positive	1	b	1.6	3–13	Recovery, complete	yes	"Moribund" on entry; prompt improvement on streptomycin (see figure 1).
2	4 mos.	Penicillin + sulfadiazine, 3 days	6	200	5	30	5	Sulfadiazine	—	0	*	0.8	3–6	Recovery, complete	?	Afebrile 5th day; secondary bout of fever for 11 days, cause not determined.
3	6 mos.	Sulfadiazine + antiserum, 5 days	9	500	14	50	15	Penicillin and sulfadiazine	—	1	b	3.1	3–6	Recovery, complete	0	Prompt improvement only after streptomycin was started.
4	6 mos.	Penicillin + sulfadiazine, 1 day	7	500	2½	50	2	Sulfadiazine 1 day	Positive	1	b	—	3	Died	—	Convulsions for several days before treatment was started; no clinical improvement. No autopsy.
5	7 mos.	Penicillin + sulfadiazine, 1 day	1	1200	3	25	3	None	Negative	0	—	—	—	Recovery, complete	0	Organisms identified at another hospital, seen in smears but cultures negative before streptomycin. Prompt improvement.
6	8 mos.	None	2	800	16	25	8	None	Positive	1	b	1.6	3–10	Recovery, complete	?	Prompt improvement. Afebrile after fifth day of therapy. (Previously reported[37])
7	9 mos.	Penicillin + sulfadiazine, 1 day	3	800	10	50	10	None	Positive	1	b	3.1	2	Recovery, complete	yes	Marked clinical improvement with subsidence of fever in 6 days.
8	9 mos.	None	6	500 800	4 7	50	12	Penicillin. Sulfadiazine later	Positive	1	b	0.8	6	Recovery; probably deaf and blind	yes	Three bouts of fever; first ended with clinical improvement on 6th day; second ended when streptomycin was stopped; last (cause undetermined) subsided on sulfadiazine therapy.

TABLE II—*Continued*

Case	Age	Previous Therapy	Streptomycin Therapy					Other Therapy	Blood Culture Before Streptomycin	Days from First Dose until C.S.F. Cultures Were All Negative	*H. influenzae*		C.S.F. Levels, Units per Ml.	Outcome	Secondary Fever Attributable to Streptomycin	Remarks on Clinical Course
			Day Begun	Intramuscular		Intrathecal					Type	M.I.C.				
				Mg. per Day	Days	Mg. per Day	Days									
9	11 mos.	Penicillin 1 day, sulfadiazine 4 days	5	500	7	50	6	None	—	1	b	3.1	2–6	Recovery, complete	0	No effect from other therapy; prompt improvement after streptomycin was given.
10	11 mos.	Penicillin + sulfadiazine + antiserum, 10 days	12	800	6	25	3	None	—	1	b	—	—	Recovery, complete	0	Relapse after antiserum and during sulfadiazine therapy. Gradual improvement after streptomycin was started. (Previously reported[87])
11	18 mos.	Penicillin + sulfadiazine, 1 day	3	1000	7	50	7	Sulfadiazine, 2 days	Negative	12 hrs.	b	3.1	2	Recovery, complete	yes	Rapid improvement, afebrile first time on third day of streptomycin.
12	18 mos.	Penicillin 1 day, sulfadiazine 3 days	4	500	9	50	9	None	Negative	1	b	1.6	2–6	Recovery, complete	0	Slow improvement, secondary fever with pharyngitis responded to sulfadiazine (figure 2).
13	2 yrs.	Penicillin + sulfadiazine, 1 day	3	1000	8	50	8	Sulfadiazine after 6 days	Positive	1	b	0.4	3–6	Recovery, complete	0	Improvement and drop in fever over 5 days; secondary fever with otitis responded to sulfadiazine.
14	2 yrs.	Sulfadiazine, 1 day	4	1000	8	50	7	Sulfadiazine after 4 days	—	1	b	1.6	2–6	Recovery, complete	0	Improved and afebrile third day; otitis and tonsillitis (*Staph. aureus*) later, improved during sulfadiazine therapy.
15	5 yrs.	Penicillin + sulfadiazine, 12 hours	1	1200	6	50	6	None	—	12 hrs.	b	3.1	3–6	Recovery, complete	yes	Improved and afebrile by fourth day.
16	4 yrs.	Penicillin + sulfadiazine, 1 dose each	1	2000 1333	2 6	50	5	None	Positive	12 hrs.	b	0.8	—	Recovery, complete	?	Diffuse macular rash, 6th and 7th days. Also severe local reaction to Schick test 4th to 12th day.

* Organism did not react with available diagnostic typing sera.
M.I.C. = Minimum inhibiting concentration (complete) of streptomycin in units per ml.[57]
C.S.F. = Cerebrospinal fluid.
— = Not done.

spinal fluid of a child with meningitis during streptomycin therapy. Following recovery by the use of sulfadiazine and specific antiserum the child continued to harbor the resistant organism in the nasopharynx over a period of one year. The epidemiological implications of this observation are obvious.

Alexander [52, 54] has also shown that cultures of *H. influenzae* which have not been previously exposed to streptomycin may contain some organisms which are apparently innately resistant to streptomycin. By inoculating large numbers of organisms into Levinthal agar containing graded dilutions of streptomycin she found organisms resistant to 1000 units per ml., though by ordinary sensitivity studies the strain would appear to be completely inhibited by 1 to 3 units of streptomycin per ml. The incidence of these streptomycin resistant organisms varied from 1 in 1.1 billion to 1 in 13.8 billion organisms. Klein and Kimmelman [55] demonstrated similar findings among strains of Shigellae, and Miller [56] in strains of meningococci.

The occurrence of secondary complicating infections during streptomycin therapy of influenzal meningitis by organisms relatively insensitive to streptomycin was described by Weinstein.[44] Three of his nine cases developed complicating staphylococcal infections while receiving streptomycin. One of them died of staphylococcal pneumonia despite penicillin therapy; the second had meningitis and the third otitis media and both of the latter recovered after penicillin was given.

Case Reports

At the Boston City Hospital, 16 infants and children with meningitis due to *H. influenzae* have been treated with streptomycin and all but one of them have recovered. The pertinent findings in all of these cases are listed in table 2. The details of the course and treatment in Cases 1 and 12 are shown in figures 1 and 2, respectively. Cases 6 and 10 were included in a previous report.[57]

The ages ranged from four months to five years and 10 of the patients were less than one year old. Blood cultures were done before streptomycin was started in 10 patients and were positive in seven. It was the practice to discontinue other medications when streptomycin was begun though in the severely ill patients this was not always done. In 15 patients there was a satisfactory response to streptomycin with prompt disappearance of the organisms from the cerebrospinal fluid. The clinical response of these patients was fairly rapid, improvement usually occurring during the first 24 to 72 hours of therapy. This improvement was manifested by a return to a normal state of consciousness, cessation of convulsions and irritability and return of the ability to feed properly. The subsidence of the fever was somewhat slower than the other clinical and laboratory evidence of improvement; the temperature did not usually reach normal for a period of four to seven days.

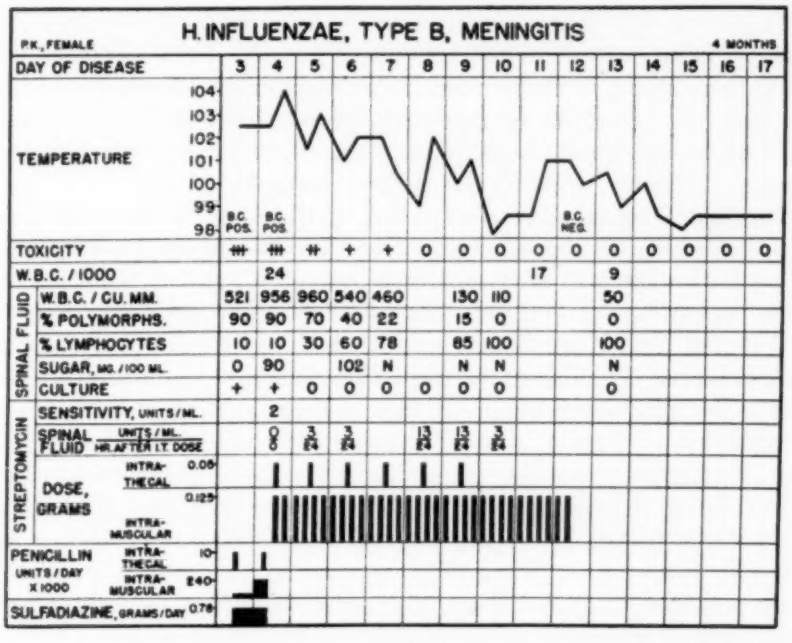

FIG. 1. *Case 1.* Subsidence of fever by the fifth day of therapy coincided with clinical improvement. A second febrile episode ended after intrathecal streptomycin was discontinued and a third after the intramuscular injections were stopped. Recovery thereafter was uneventful.

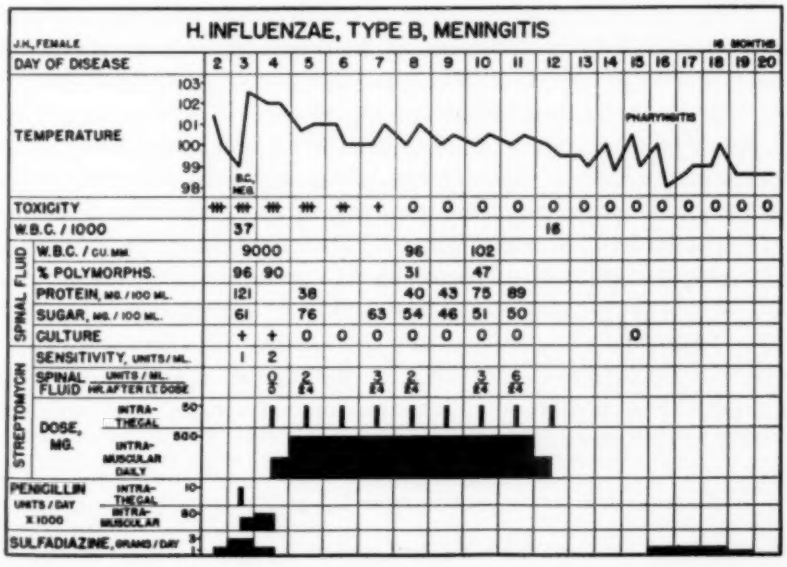

FIG. 2. *Case 12.* The temperature remained moderately elevated throughout the period of streptomycin therapy and despite prompt and continued clinical improvement. There was also a slight secondary increase in the protein of the cerebrospinal fluid toward the end of therapy. Pharyngitis with fever appeared after streptomycin was stopped and cleared promptly with the use of sulfadiazine. There were no other complications.

The patient who did not respond to streptomycin (Case 4) was a six month old infant who had had convulsive seizures for several days before entering the hospital. Streptomycin was begun on the seventh day of illness and cultures of the cerebrospinal fluid were negative thereafter. There was no clinical improvement, however, and death occurred on the third day of therapy. The cause of death was not determined.

Neurological sequelae were noted only in Case 8. In this nine month old infant treatment was begun on the sixth day of the disease and following recovery the patient was deaf and blind.

The appearance of resistant strains of *H. influenzae* was not demonstrated in this series. It is not possible, however, to rule out the presence of such resistant organisms in some localized areas of infection in the fatal case even though the cerebrospinal fluid cultures were negative before death.

Complicating infections, notably acute pharyngitis and otitis, occurred during or after the course of streptomycin therapy in four patients and possibly in a fifth. It was not always possible to identify the causative organisms in these infections. The institution of sulfadiazine, however, was followed by subsidence of fever and symptoms in each instance.

The occurrence of secondary fever after an initial response to therapy suggests one of at least four possibilities: (1) a relapse of the original infection, (2) focal purulent complications such as a brain abscess, (3) a secondary complicating infection by another organism or (4) drug fever. Obviously, the proper interpretation of the secondary fever is very important. In the present series, secondary fever, apparently related to the streptomycin, appeared in five patients and possibly in three others. In these cases the secondary fever subsided promptly after the streptomycin was stopped.

The course of the cases with streptomycin fever is of interest. The initial fall in temperature occurred between the fourth and seventh day of therapy and was accompanied by clinical and laboratory evidence of improvement. A secondary rise in temperature occurred shortly thereafter and continued as long as the streptomycin was given. The clinical and laboratory evidence of improvement continued in these cases in spite of this fever. In most of the patients both the intramuscular and the intrathecal injections were stopped at about the same time. In Case 1, however, there were two febrile episodes, the first subsiding when the intrathecal injections were stopped and the second only after the intramuscular injections were discontinued. The course in this case is shown in figure 1.

Meningitis Due to Other Gram-Negative Bacilli

Infections of the central nervous system by gram-negative bacilli other than *Hemophilus influenzae* are infrequent. The coliform organisms are the ones most often implicated.[58] The incidence of meningitis due to coliform bacteria is highest in infants under three months,[1, 7, 11, 59] suggesting a

low degree of resistance to such infections in this age group.[58, 60] The other gram-negative bacilli which are less often encountered as the cause of meningitis may occur in any age group, and comprise a wide variety of organisms including *Alkaligenes fecalis,*[53] *Aerobacter aerogenes,*[58] *Klebsiella pneumoniae,*[1, 61, 62] *Pasteurella tularensis,*[63] *Proteus morgani* and *Proteus vulgaris,*[55, 64, 65] *Pseudomonas aeruginosa,*[66] the salmonella group,[1, 67] *Serratia marcescens*[68] and others.

Meningitis caused by these organisms usually occurs by direct extension from an adjacent focus of infection in the paranasal sinuses, ear, mastoid, a brain abscess or a meningocele. It may follow skull fractures or contaminated lumbar puncture or spinal anesthesia procedures.[12, 57, 58, 64, 66, 69] It may also arise by hematogenous spread from a distant focus of infection; cases of coliform meningitis in infants seem to arise largely in this manner.[7, 11, 58]

The use of sulfonamides has resulted in some lessening of the mortality in this type of meningitis but such infections are still quite serious and penicillin apparently has little to offer.[57, 63, 66, 67, 70-72] The outcome in some of these cases may also depend on successful surgical drainage of purulent foci of suppuration.*

Several authors have reported on the use of streptomycin in meningitis due to this group of gram-negative bacilli. The pertinent findings in their cases are listed in table 3. Though the over-all mortality in this group of cases is high (45 per cent), it is probable that in many of these patients as in those of influenzal meningitis, treatment with streptomycin was begun late and only after therapy with other agents had failed.

Streptomycin has been shown to be active in vitro against most of these gram-negative bacilli and it is effective in experimental infections of animals with some of them.[40] The early institution of intramuscular and intrathecal streptomycin when combined with surgery wherever indicated should, therefore, go far towards lowering the mortality rates in meningitis due to these organisms. Inasmuch as systemic infections with Brucella and Salmonella, including typhoid fever, have not responded favorably to streptomycin, its effects in meningitis due to these organisms cannot be predicted. Streptomycin should, nevertheless, receive a trial in these infections.

* A recent report[101] records 12 fatal cases of meningitis following penetrating wounds of the cranium and the spinal canal. Seven of the deaths were attributable to *Klebsiellae,* three to *Aerobacter aerogenes* and one each to *B. coli* and a Shigella. Four additional patients with superficial infections of the brain with *K. pneumoniae* not involving the ventricles survived in 10 of these 16 cases including all of the survivors, there was a mixed infection with gram-positive organisms. All were treated intensively with sulfonamides and penicillin and one who recovered was also given chloral hydrate intrathecally.

Another recent case[102] of interest is that of a month old infant in whom an *A. aerogenes* meningitis and septicemia cleared completely following treatment with penicillin and sulfathiazole. The infant subsequently died of an underlying bilateral hydronephrosis and pyelonephritis shortly after treatment with streptomycin was started. The latter infection was due to *E. coli* and no evidence of the meningitis was found at autopsy.

TABLE III

Meningitis Due to Gram-Negative Bacilli Other Than *Hemophilus influenzae*
Summary of Reported Results in Streptomycin-Treated Cases

Author	Number of Cases	Organism	Previous Treatment	Concomitant Treatment	Streptomycin*				Result		Remarks
					Intramuscular		Intrathecal		Recovered	Died	
					Mg. per Day	Days	Mg. per Day	Days			
DeBakey and Pulaski[65]	1	*A. aerogenes*	—	—	—	—	—	—		1	Adult. Infection followed laminectomy. Moribund when treatment was begun. Died 9½ hours after first dose.
Edwards and Kirk[74]	1	*A. cloacae*	Streptomycin, intramuscular	—	1000–1500	36	0			1	Adult. Meningitis developed during intramuscular streptomycin therapy for osteomyelitis of ilium with bacteremia. Organism became resistant to streptomycin.
Cairns et al.[45]	1	An achromobacterium	—	Penicillin, sulfonamides	0		80	2	1		Organisms not found after first injection of streptomycin.
N.R.C.[55]	4	*Alk. fecalis*	*	*	500	9	100	6	4		Three of these patients listed as "improved."
Alexander[75]	1	*E. coli*	Penicillin	None	1600 1000	4 12	50	13	1		Adult. Infection followed spinal anesthesia for reamputation of foot. No organisms found after 4th day of treatment.
N.R.C.[55]	3	*E. coli*	*	*	500	9	100	6	3		Two of these patients listed as "improved."
Zantiny and Carlson[47]	1	*E. coli*	None	None	800	12	0		1		23-day old infant. Infection followed operation on congenital meningocele, C.S.F. cultures negative 48 hours after streptomycin was begun.
Shields[76]	1	*E. coli*	Penicillin and sulfadiazine	None	240	10	30	10	1		5-week old infant. Cultures of C.S.F. negative after 2d day of treatment. No sequelae.
DeBakey and Pulaski[65]	1	*E. coli*	—	—	—	—	—	—	1		
N.R.C.[55]	2	*K. pneumoniae*	*	—	500	9	100	6		2	
Tartakoff et al.[52]	1	*K. pneumoniae*	Penicillin and sulfadiazine	—	3000	3	50 intracisternal	3		1	Adult. Meningitis followed craniotomy. Culture of C.S.F. negative on 7th day of disease when streptomycin was started.
Hough and Adelson[102]	1	*K. pneumoniae*	—	Penicillin and sulfathiazole	150	7	50	1		1	29 years old. Post abortive septicemia and meningitis. *K. pneumoniae*, type B, cultured from blood, cerebrospinal fluid and uterus at autopsy.

TABLE III—*Continued*

TABLE III—*Continued*

Author	Number of Cases	Organism	Previous Treatment	Concomitant Treatment	Streptomycin*				Result		Remarks
					Intramuscular		Intrathecal		Recovered	Died	
					Mg. per Day	Days	Mg. per Day	Days			
N.R.C.[58]	1	*P. morgani*	*	*	500	9	100	6	1		
N.R.C.[62]	2	*P. vulgaris*	*	*	500	9	100	6	1	1	
DeBakey and Pulaski[65]	1	*P. vulgaris*	—	—	—	—	—	—	1		
N.R.C.[58]	2	Salmonella	*	*	—	—	—	—	1	1	
Barnes[77]	1	*S. cholerae suis*	Penicillin and sulfamerazine	—	60	6	100 intracisternal	6		1	Newborn. Streptomycin begun on 20th day of disease. Improved clinically, but C.S.F. cultures remained positive.
Massengale[78]	1	*S. schottmülleri*	Penicillin and sulfadiazine	Sulfadiazine	400	1½	0		1		Newborn. Treatment begun late. C.S.F. cultures became negative. Died about 1 month later of hydrocephalus.
Cairns et al.[45]	3	*Ps. aeruginosa*	Penicillin and sulfonamides	—	0		(1) 80 (2) 50 (3) 100	13 4 2		3	Streptomycin given intraventricularly to 2 patients. All very ill at start of treatment.
DeBakey and Pulaski[65]	1	*Ps. aeruginosa*	—	—	—	—	—	—	1		
Stanley[66]	1	*Ps. aeruginosa*	Penicillin, streptomycin and sulfadiazine	Sulfadiazine	2000	5	0			1	17 years old. *B. pyocyaneus* sepsis complicating disseminated lupus treated with streptomycin subcutaneously. Meningitis developed during streptomycin therapy.
Merwarth et al.[101]	1	*Ps. aeruginosa*	Penicillin and sulfadiazine	Sulfadiazine 7 days	1000	15	50–100	15	1		23 years old. Meningitis followed spinal anesthesia. Vertigo during treatment. Flaccid paraplegia developed 3 weeks later and was attributed to neurotoxic reaction to streptomycin.
Morgan and Hunt[46]	1	Gram-negative bacillus unidentified	—	—	—	—	—	—		1	Meningitis followed craniotomy. Intrathecal and intramuscular streptomycin resulted in fall in temperature and disappearance of organism from C.S.F. Spinal block developed and patient died. Organism cultured from cerebellar abscess at autopsy resistant to 1000 units; pretreatment strain inhibited by 2 units.
Totals	33								18	15	

— = Data not given.

* = Most of the patients included from the N.R.C. report received penicillin and sulfonamides before and some also during streptomycin therapy. The streptomycin doses in those cases are averages.

Note: DeBakey and Pulaski's cases[65] have been reported in greater detail by Pulaski and Matthews[104] who added 2 cases, 1 due to *E. Coli* and the other to *K. pneumoniae;* both recovered after treatment with streptomycin, penicillin and sulfadiazine.

TABLE IV

Cases of Meningitis Due to Organisms Other Than *Hemophilus influenzae* That Were Treated with Streptomycin at the Boston City Hospital

Case	Age	Previous Therapy	Organism	M.I.C., Units per Ml.	Streptomycin Therapy					C.S.F. Levels, Units per Ml.*	Other Therapy	Days from First Dose until C.S.F. Cultures Were All Negative	Outcome	Secondary Fever Attributable to Streptomycin	Remarks on Clinical Course
					Day Begun	Intramuscular		Intrathecal							
						Mg. per Day	Days	Mg. per Day	Days						
17	38 yrs.	Penicillin, 4 days, sulfadiazine, 20 days	*Aerobacter aerogenes*	13	20	4000	10	200–50	10	3–50	None	1	Recovered	yes	Details shown in figure 3.
18	2 mos.	Penicillin, 14 days	*Escherichia coli communis*	6	?	500	½	50	½	—	Sulfadiazine	Cultures remained positive	Died	—	Moribund with positive blood culture before treatment and after severe intractable diarrhea (etiology unknown). Died after 2 injections. C.S.F. cultures remained positive and organism remained sensitive.
19	57 yrs.	Penicillin + sulfadiazine, 2 days	*Hemophilus parainfluensae*	6	3	4000	10	100 50	3 5	3–25	Penicillin + sulfadiazine	1	Recovered; ataxia	yes?	Followed skull fracture. Loss of vestibular reflexes began on tenth day and was complete; postural compensation was almost complete in 3 weeks.
20	20 yrs.	Penicillin + sulfadiazine, 19 days	"Pleuropneumonia"	25	19	4000	7	50	10	3–25	Penicillin + sulfadiazine	11	Recovered	0	Brain abscess and meningitis after stem of "smoking" pipe was thrust through orbit. Marked clinical improvement coincided with start of streptomycin. Details to be reported elsewhere.
21	4 mos.	Penicillin, 6 days, sulfadiazine, 2 days	*Proteus morgani*	50	6	400	10	50 into meningocele	7	20–160	None	1	Recovered	yes	Followed operation on meningocele. No complications. (Case 3 in reference 57.)
22	11 days	Penicillin, 4 days	*Pseudomonas aeruginosa*	50	4	200	36	25–50 intraventricular	15	16–100	None	27	Recovered; rt. facial paralysis	yes	Followed surgical debridement of infected meningocele. Clinical improvement before cultures were negative. (Case 2 in reference 57.)
23	12 days	Penicillin, 2 days	*Pseudomonas aeruginosa*	25	3	200	23	10 25	13 10	2–3 6–50	Penicillin intramuscularly	Cultures remained positive	Died	0	Details of the course and therapy are shown in figure 4.
24	14 yrs.	Penicillin + sulfadiazine, 3 days	*Pseudomonas aeruginosa*	13–50	4	4000	7	50	8	3–25	Sulfadiazine	4	Recovered	yes	Meningitis followed lumbar puncture. No complications. (Case 1 in reference 57.)

* 24 hours after previous intrathecal injection except in Case 17 in which most of the levels were obtained after 12 hours.

Case Reports

At this hospital eight patients with meningitis due to gram-negative bacilli, other than *H. influenzae*, have been treated with streptomycin and six of them have recovered. There were three patients with meningitis due to *Pseudomonas aeruginosa* (*Bacillus pyocyaneus*), and one patient each with meningitis due to *Proteus morgani, Aerobacter aerogenes, Escherichia coli communis, Hemophilus parainfluenzae* and a "pleuropneumonia-like" organism. Some of the relevant details of these cases are listed in table 4, and the clinical and laboratory findings in Cases 17 and 23 are shown in figures 3 and 4, respectively. Three of the cases have been reported previously.[57]

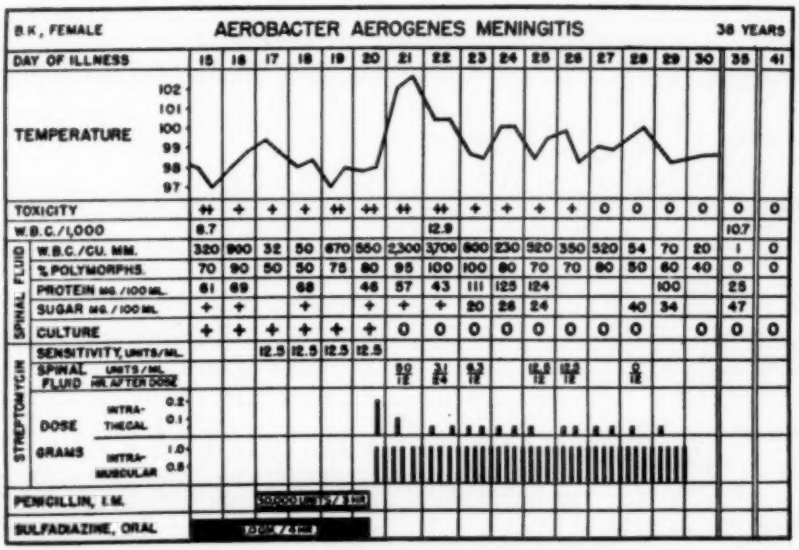

FIG. 3. *Relevant findings in Case 17.* The meningitis began while the patient was receiving sulfadiazine prophylactically for a skull fracture and persisted after intramuscular and intrathecal penicillin was added to the treatment. (The latter is not shown in the chart.) Cultures of the cerebrospinal fluid became negative after the first intrathecal dose of streptomycin and remained so. There was a sharp febrile reaction, with increase in signs of meningeal irritation and also in the cellular and protein content of the cerebrospinal fluid after the initial intrathecal injection of 200 mg. of streptomycin. The increased pleocytosis continued when 100 mg. were given but the reaction subsided when the intrathecal doses were reduced to 50 mg. each. Recovery was uneventful.

The pathogenesis of these cases is of interest. In three patients the meningitis was secondary to trauma to the head; in three others it was secondary to infection of a congenital meningocele; one case followed a diagnostic lumbar puncture and in another the meningitis was associated with a bacteremia.

Penicillin with or without sulfadiazine had been given to all of these patients without effect before the institution of streptomycin. Moreover, in Case 18 the meningitis developed during penicillin treatment for diarrhea

and in Case 19 it began during prophylactic administration of sulfadiazine and penicillin following a fracture of the skull. One or both of these agents was also given during the streptomycin administration in five of the patients.

There were two deaths in this group of eight patients. One of these deaths was in a 12-day old infant and followed the development of streptomycin resistance by the infecting organism (Case 23, see figure 4). The other (Case 18) occurred after only 12 hours of treatment in an infant who was moribund when the streptomycin was started.

There was evidence of clinical improvement shortly after streptomycin was begun in all of the patients who recovered. In three of them, however, organisms persisted in the cerebrospinal fluid for a varying number of days

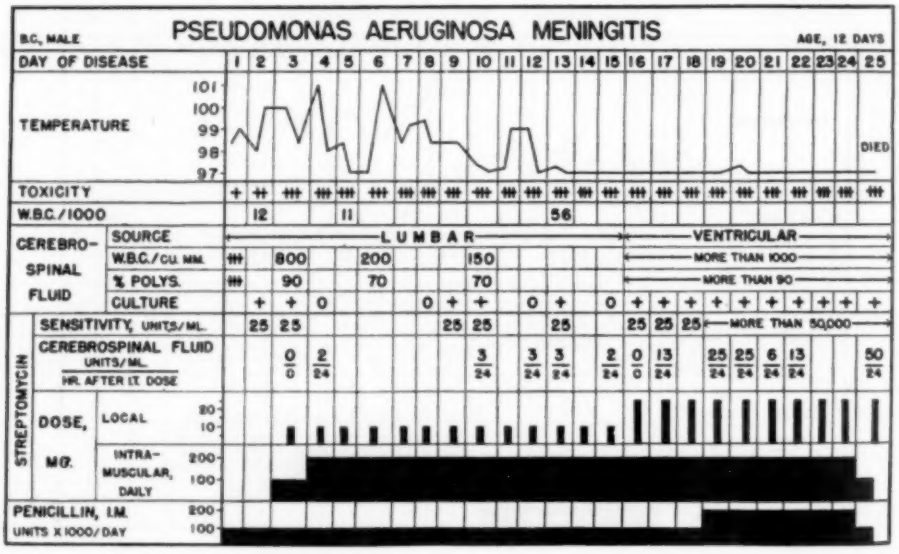

FIG. 4. *Course and relevant findings in Case 23.* The meningitis followed erosion and infection of a congenital meningocele. There was no clinical improvement on streptomycin and the course was steadily downward in spite of subsidence of fever. Cultures of the cerebrospinal fluid remained positive. Injections were given into the lateral cerebral ventricles through the anterior fontanelle after a block developed. There were frequent convulsions before that time but not thereafter. The organisms obtained after the sixteenth day of treatment were all completely resistant to streptomycin.

during streptomycin treatment. Secondary fever attributable to streptomycin occurred in four and possibly a fifth patient; in these cases, as in those due to *H. influenzae*, clinical and laboratory evidence of improvement continued during the secondary febrile episode. There were no complicating infections with other organisms in any of these cases. The only residual neurologic damage among those who recovered was a right facial palsy in Case 22. As already noted, a resistant strain appeared during treatment in one patient, Case 23, and that patient died. In another patient, Case 20, the organism was recovered from the cerebrospinal fluid throughout the

period of treatment; the organism retained its original sensitivity for six days and was resistant during the last four days. The organism then disappeared from the spinal fluid and the patient recovered.

Tuberculous Meningitis

The frequency with which *Mycobacterium tuberculosis* involves the meninges may be noted in table 1. Infants and children are affected more often than adults. Tuberculous meningitis probably arises in most cases by hematogenous spread from a focus of infection elsewhere in the body though in some cases it occurs by direct extension from a tuberculous lesion of the brain. Prior to the use of streptomycin tuberculous meningitis was a uniformly fatal disease.

Streptomycin was early shown to be effective against *M. tuberculosis* in vitro,[79] and in experimental infections in animals.[80] The in vitro sensitivity of a large number of strains of *M. tuberculosis* isolated from cases of human infection was found to be less than 1 unit per ml.[79, 81–83]

Reports are now available in 32 cases of tuberculous meningitis that have been treated with streptomycin.[65, 84–91] At the time when they were reported, 13 of this group of patients were still living. The incidence of permanent neurologic damage was high, however, and the survivors had been followed for only short periods after cessation of streptomycin therapy. The remarkable fact was that they were alive and that their disease was apparently arrested. Histopathological findings in fatal cases have also given evidence of the effectiveness of streptomycin in such cases.[92]

Of considerable interest is the fact that parenteral therapy alone has proved inadequate in these cases. Two patients were noted to develop signs of meningitis during intramuscular streptomycin therapy for miliary tuberculosis and the meningitis apparently responded only after streptomycin was also given intrathecally.[53] The four survivors among the seven patients treated by Hinshaw and his co-workers [90] all received both intramuscular and intrathecal therapy while the fatal cases received the drug only intramuscularly. A prolonged period of combined parenteral and intrathecal streptomycin seems indicated in this condition.[90]

The appearance of streptomycin resistant strains of *M. tuberculosis* has not been reported as occurring specifically during therapy of tuberculous meningitis but resistant strains have appeared frequently in patients with pulmonary tuberculosis while on streptomycin therapy.[90, 93, 94] There is no reason to believe that similar resistant strains will not also be noted during the streptomycin treatment of meningeal tuberculosis.

Case Reports

Three patients with tuberculous meningitis have been treated with streptomycin at the Boston City Hospital. In each instance the diagnosis was proved by guinea pig inoculation of cerebrospinal fluid obtained just prior

to institution of therapy. Streptomycin was given intrathecally and intramuscularly to all three patients. There was one death in this group. A brief description of the three cases follows:

Case 25. Treatment was begun in this seven year old child approximately 10 days after the onset of symptoms. Streptomycin was given intramuscularly, 0.5 gm. daily in divided doses, for 142 days. It was also given intrathecally throughout this period—25 mg. daily for the first 45 days, and 50 mg. every other day for the next 20 days and twice weekly thereafter. There was progressive improvement in the clinical condition of the patient over a period of about a month. During the daily intrathecal injections of streptomycin, however, there was a gradual rise in the protein content of the cerebrospinal fluid and it fell again only when the injections were given at longer intervals. Tubercle bacilli were recovered from the cerebrospinal fluid by guinea pig inoculation before streptomycin was started and again after four days of therapy, but thereafter all guinea pig inoculations were negative. There was slight residual weakness in the left arm and the left leg at the conclusion of treatment but there were no other neurologic defects and psychiatric examination revealed no evidence of mental impairment. When examined two months after the streptomycin was stopped the patient was continuing to improve.

Case 26. Streptomycin was started in this 10 month old infant one week after the onset of symptoms and has been continued over a period of 3½ months. The dosage used was 125 mg. intramuscularly every six hours and intrathecal injections of 50 mg. each given daily for 40 days and twice a week thereafter. The intrathecal injections were given first by the lumbar route and later into the lateral cerebral ventricles through the anterior fontanelle. There were occasional convulsions during the period of daily intraventricular injections but these subsided when the injections were given twice a week. The cerebrospinal fluid protein has remained elevated in this case. The infant has improved clinically and the temperature has gradually returned to normal. At the present time the infant seems blind but there is no other obvious neurologic damage. Guinea pig inoculations of the cerebrospinal fluid were positive before the streptomycin was started and have been negative since then.

Case 27. This 2½ year old child had symptoms for approximately two weeks before treatment was begun. Streptomycin was given in doses of 250 mg. every six hours and 50 mg. intrathecally once each day for 17 days. There was no apparent clinical improvement and the patient died. There was no autopsy.

The ideal drug for the treatment of tuberculosis is not yet at hand. Streptomycin is undoubtedly the best one available at present but it has many shortcomings, particularly the ease with which organisms may become resistant to it. A trial of the simultaneous use of streptomycin with one of the sulfone drugs such as Promin, Diasone or Promizole, in the treatment of tuberculosis certainly seems indicated since such a combination appears to be more effective than the use of either alone in experimental infections in animals.[95, 96]

Untoward Reactions

Fever was the most frequent untoward reaction from streptomycin noted in the patients treated for meningitis at the Boston City Hospital. A secondary febrile episode attributable to the streptomycin occurred in nine patients, and possibly in four others, among the 24 nontuberculous cases. Such a

reaction was more difficult to interpret in those with tuberculous meningitis. In some of the cases the secondary fever may have been related chiefly to the intrathecal injections since the fever subsided promptly when those injections were discontinued. Furthermore, the fever in some of them was associated with a secondary increase in the cellular and protein content of the cerebrospinal fluid. In one patient the fever again recurred following the discontinuance of intrathecal therapy and persisted until the intramuscular injections were stopped.

An increase in the protein content of the cerebrospinal fluid not associated with an increase in the number of cells was noted in two patients with tuberculous meningitis while they were receiving daily intrathecal injections over a long period. The protein level slowly fell when the intrathecal injections were spaced at longer intervals.

The largest single intrathecal dose of streptomycin was 200 mg. given initially in Case 23. Shortly after this injection, the patient exhibited transient irritability and some clonic movements of the lower extremities and this was followed by a marked rise in temperature. Cerebrospinal fluid removed 24 hours after this injection showed a marked increase in the number of leukocytes, mostly polymorphonuclears, and there was also a moderate increase in protein. The cerebrospinal fluid findings gradually returned toward normal when the size of the intrathecal dose was decreased.

Ataxia was observed only in Case 19. It was first noted on the tenth day of streptomycin therapy. Caloric and rotation tests showed complete absence of vestibular response in this case but the patient was gradually able to compensate for this defect. There was some loss of hearing at this time but its relation to the therapy could not be evaluated.

One patient (Case 16) developed a macular, erythematous rash on the sixth day of streptomycin therapy. The rash cleared in about 48 hours coincident with discontinuance of the streptomycin. There were no other reactions referable to other organs in any of the patients.

Discussion

The findings in the present cases indicate that streptomycin is of considerable value in the treatment of meningitis due to gram-negative bacilli. The drug should be given both intramuscularly and intrathecally. In adults an intramuscular dose of 1 gm. every six hours and a single daily intrathecal injection of 50 mg. appears to be adequate for most cases. Somewhat larger doses, 1 gm. every four hours intramuscularly and 50 to 100 mg. intrathecally twice a day for one or two days, may be given but are probably not necessary in most cases. Infants and small children may be given about 25 mg., or slightly more, per pound of body weight per day intramuscularly and 10 to 50 mg. daily by the intrathecal route.

Most cases of meningitis due to gram-negative bacilli seem to respond well to streptomycin alone if the treatment is started early in the course of

the disease. If treatment is begun late, however, or if the patient is severely ill when the treatment is started, sulfadiazine should probably be given in addition. Likewise, in cases due to *H. influenzae* type b, specific antiserum and sulfadiazine should also be given under similar circumstances. The possibility of inhibiting the development of streptomycin resistant strains by the combined use of sulfadiazine and streptomycin has been suggested.[97] Penicillin should also be used whenever an infection with a susceptible organism is present or suspected. The possible use of large doses of penicillin specifically for their effect on certain gram-negative bacillus infections warrants further exploration.

In tuberculous meningitis, the early and persistent use of streptomycin may offer the only hope of arresting the disease. It is essential that cerebrospinal fluid be obtained for culture or guinea pig inoculation, or both *before* streptomycin is started since these procedures may later yield negative results and leave the diagnosis in doubt. The streptomycin should be given in these cases both intramuscularly and intrathecally over a period of three or possibly four months. The doses required in cases of tuberculous meningitis may be somewhat smaller than those used in infections with gram-negative bacilli due to the greater sensitivity of the strains of *M. tuberculosis*. The intrathecal doses should be given daily for three to five weeks and at gradually increasing intervals up to twice weekly thereafter.

Excessively large individual doses by intrathecal injection should be avoided in all cases. They are known to produce serious reactions in animals[98] and in humans.[45, 99] It appears likely that the concentration of streptomycin in the solution injected as well as the total amount may be an important factor in these reactions as has been suggested in the case of penicillin.[100]

Summary and Conclusions

Streptomycin has been used in the treatment of 27 cases of meningitis at the Boston City Hospital. There was one death among 16 cases due to *Hemophilus influenzae* and two deaths among eight cases due to other gram-negative bacilli. The deaths occurred in two patients in whom treatment with streptomycin was begun late in the disease and in the third it was associated with the development of a streptomycin resistant strain of *Pseudomonas aeruginosa* during treatment. Two of three patients with tuberculous meningitis are living and their disease appears to be arrested.

The results in these cases and in similar cases reported by others seem to justify the following conclusions:

1. Streptomycin is the only agent now available which may arrest the progress of tuberculous meningitis.

2. Streptomycin is the most effective single agent in the treatment of meningitis due to gram-negative bacilli, including *Hemophilus influenzae*.

Addendum. The following is a summary of eight cases of meningitis treated with streptomycin since this paper was submitted.

1. A case of *H. influenzae,* type b meningitis in an infant one year old was treated with streptomycin, 50 mg. intrathecally once a day and 200 mg. intramuscularly every six hours for a total of seven days. The organism was sensitive to 3.1 units. Sulfadiazine was also given during this time. The patient responded promptly and recovered without complications.

2. In a second case of *H. influenzae,* type b meningitis in a 15-month old girl, cultures of the cerebrospinal fluid were still positive after two days of treatment with sulfadiazine. Streptomycin was given as in the previous case. A single dose of specific antiserum was also given 24 hours after the streptomycin was started but the temperature had already dropped and smears and cultures of the cerebrospinal fluid were already negative at that time. The organism was sensitive to 3.1 units. Recovery was rapid, complete and uncomplicated.

3. A case of *E. coli communis* meningitis in a five day old infant with an infected lumbar meningocele was treated with streptomycin for a total of 20 days in doses of 60 mg. every six hours intramuscularly, and 25 mg. were injected daily into alternate cerebral ventricles through the anterior fontanelle. The latter dose was reduced to 10 mg. after 14 days because of persistently high protein levels in the cerebrospinal fluid. Cultures of the cerebrospinal fluid were positive before streptomycin was started in spite of previous penicillin and sulfadiazine therapy, but subsequent cultures were all negative. The organism was inhibited by 12.5 units of streptomycin. Surgical repair of the meningocele was done on the tenth day and a catheter left in the ventricle for 10 days. The infant has apparently recovered without sequelae demonstrable at this time.

4. A case of *E. coli communior* meningitis of unknown duration and pathogenesis in a 68 year old woman was treated with daily doses of 50 mg. of streptomycin intrathecally and 1 gm. every four hours intramuscularly. This was supplemented by sulfadiazine and large doses of penicillin. Cultures of blood and spinal fluid were positive before and after treatment and the patient died on the fifth day. The organism obtained before the first day of streptomycin was completely inhibited by 12.5 units of streptomycin per ml. but those obtained from blood and spinal fluid 24 hours later and all subsequent ones grew uninhibited in a concentration of 50,000 units per ml.

5. A case of *K. pneumoniae,* type A meningitis of otitic origin in a woman 70 years old, was treated with streptomycin 1 gm. every four hours intramuscularly and three intrathecal doses of 50 mg. each at 12-hour intervals. The patient also received sulfadiazine orally and penicillin intramuscularly and intrathecally. The organism was obtained from cultures of cerebrospinal fluid, blood and aural discharge before treatment and was inhibited by 1.56 units of streptomycin per ml. Spinal fluid cultures were still positive 12 and 24 hours after streptomycin was started and the patient died 33 hours after the first dose.

6. An 18-month old girl with tuberculous meningitis and miliary tuberculosis, the former proved by guinea pig inoculation of spinal fluid, was given streptomycin over a period of 3½ months. Intramuscular injections of 250 mg. were given every six hours throughout this period and intrathecal injections of 25 mg. each were given daily for two weeks, then every other day for four weeks and twice weekly thereafter. There was rapid clinical improvement, the pulmonary and meningeal signs cleared and the patient was discharged at the end of the course of treatment apparently cured and without sequelae.

7. A one-year old infant with very similar findings and treated in the same manner died at the end of the fourth week without showing any definite evidence of improvement.

8. A girl 13 years old with tuberculous meningitis and miliary tuberculosis has now been under treatment for six weeks. She had had proved tuberculous arthritis for one year and symptoms of meningitis for one week before the streptomycin was started. She has received 250 mg. intramuscularly every six hours throughout and intrathecal injections of 50 mg. daily for two weeks and every other day thereafter. Clinical improvement was rapid and the patient has been free of fever and symptoms since the first week of therapy.

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PLEUROPULMONARY TULAREMIA *

By HUGH J. MORGAN, M.D., F.A.C.P., *Nashville, Tennessee*

IN a previous communication to the ANNALS OF INTERNAL MEDICINE from the Vanderbilt University Hospital, Hunt reported observations on 12 cases of pleuropulmonary tularemia treated with streptomycin during a nine months period in 1946.[1] Unfortunately, the clinical charts prepared for this publication were lost by the printer and did not appear in Hunt's article.

In the present communication selected cases from the Vanderbilt University Hospital material and 15 additional cases of pleuropulmonary tularemia treated with streptomycin in Veterans Administration Hospitals are presented in summary form and discussed briefly. For a more detailed discussion of pleuropulmonary tularemia the reader is referred to the excellent article and bibliography by Hunt.

UNCOMPLICATED ULCEROGLANDULAR TULAREMIA

This common form of tularemic infection constitutes no diagnostic problem. The occurrence of ulcer or localized inflammatory process at the site of inoculation (finger, hand, eye) with satellite bubo, a sharp febrile reaction often accompanied by chill and the history of contact exposure (most commonly by having dressed a wild rabbit during the preceding week or 10 days) leave little doubt as to the nature of the infection. The response to streptomycin therapy is prompt.

Case 1 (*Figure 1*) *D. B. Ulceroglandular tularemia.* A 17 year old colored male dressed a wild rabbit seven days before the development of an ulcer on the dorsum of the right hand, chill, fever, severe headache and prostration. A week later he was admitted to the Nashville General Hospital acutely ill. The ulcer was indurated. The right epitrochlear and axillary lymph nodes were large and tender. Fever was present. The leukocyte count was normal. The serum agglutination titer against *P. tularensis* was 1:40 and subsequently rose to 1:5120. *P. tularensis* was recovered from an epitrochlear node by mouse inoculation. The administration of streptomycin (1 gm. daily, in divided doses, for four days) was followed by prompt relief of symptoms and gradual disappearance of fever. Five days after termination of streptomycin treatment material aspirated from the epitrochlear lymph node failed to yield *P. tularensis* on mouse inoculation. The ulcer healed slowly and there was slow regression in the size of the lymph nodes. Recovery was complete.

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I am indebted to Drs. Aubrey B. Harwell and Robert C. Berson of the Thayer Veterans Hospital, Nashville, Tennessee, and the Veterans Administration, Washington, D. C., for the data on patients in Veterans Administration hospitals.

Ulceroglandular Tularemia with Complications

When in the course of ulceroglandular tularemia manifestations of infection develop elsewhere, as in the pleura, lungs, pericardium and central nervous system, there is reason for little doubt regarding the etiology of the complications. The recognition of the tularemic etiology of the ulceroglandular lesions clarifies the problem of the complications. The incidence of pleuropulmonary complications in patients with ulceroglandular tularemia who were admitted to Veterans Administration Hospitals during a nine

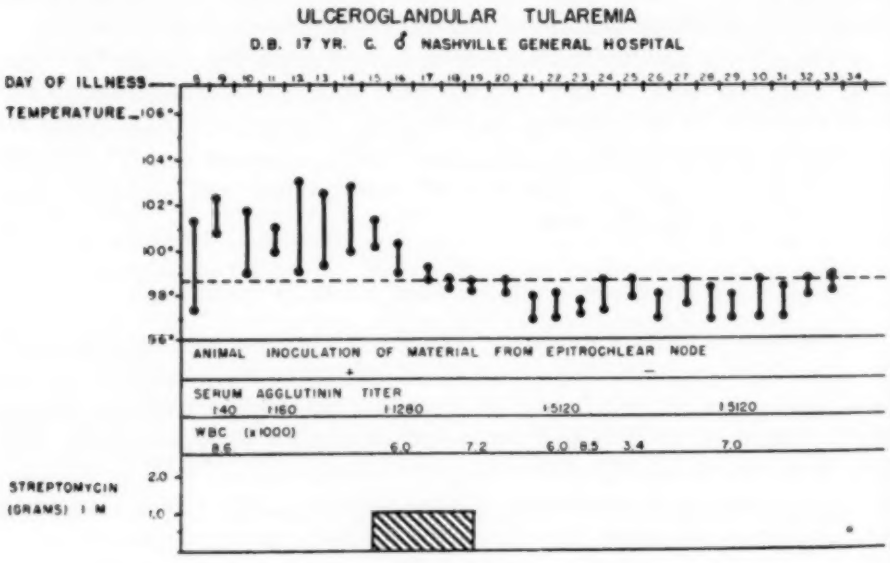

Figure 1.

months period in 1946 is indicated in table 1. They were present in more than 25 per cent of the patients. The extraordinary effectiveness of streptomycin in the presence of such complications is apparent in Cases 2 and 3. In both instances the patients were desperately ill.

Table I

Incidence of Pleuropulmonary Involvement in Tularemia
(Veterans' Administration Hospitals, 9 mo., 1946)

Pleuropulmonary Involvement	Number	Per Cent
Absent	41	73
Present	15	27
Total	56	100

Case 2. (*Figure 2*) *L. V. Ulceroglandular tularemia with pneumonia, pleural effusion and pericarditis.* A 28 year old white farmer cut his hand while dressing a wild rabbit 14 days before admission to hospital. Four days later multiple ulcers on the hand, fever and prostration developed. On the fourth day of fever, cough pro-

ductive of yellow sputum was noted and he appeared to be losing ground. On the eleventh day of illness he was admitted to the Vanderbilt University Hospital in a semi-comatose state. There was moderate dyspnea. A loud pericardial friction rub was heard and fluid was present in the left pleural cavity. There were three small, shallow, indurated ulcers on the left hand and the left epitrochlear lymph node was large and tender, as were the left posterior cervical lymph nodes. Purulent conjunctivitis was present. The spleen was palpable. The leukocyte count was 4600.

Sputum obtained on admission, before the administration of streptomycin, was injected into mice. *P. tularensis* was subsequently recovered. The patient's blood serum contained no agglutinins against *P. tularensis*.

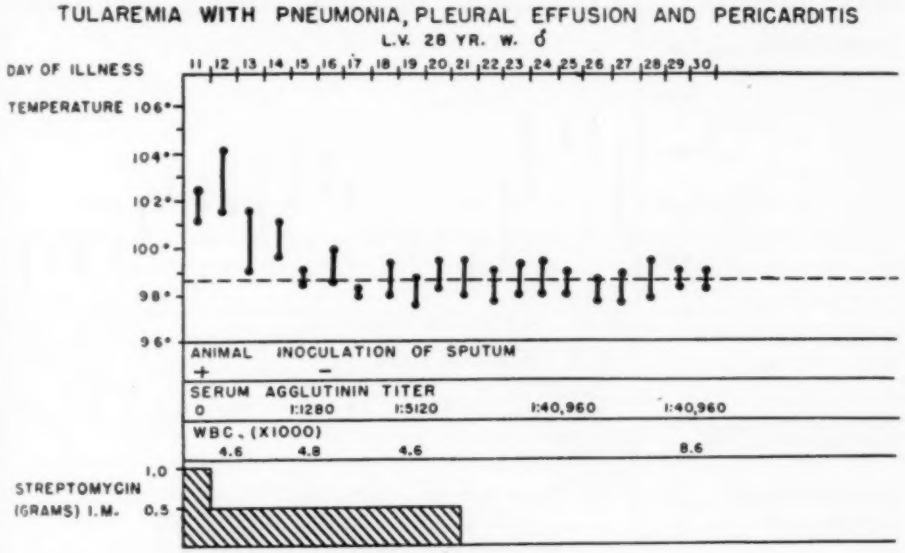

FIGURE 2.

During the first 24 hours in hospital the patient received 1 gm. streptomycin in divided doses. Within 12 hours he became mentally alert and appeared greatly improved. Streptomycin was continued in daily doses of 0.5 gm. After 48 hours the temperature declined moderately, there was striking improvement in the conjunctivitis and the lymph nodes were less tender. He coughed less and the sputum became mucoid. The pericardial friction rub disappeared. On the fourth hospital day 1250 c.c. of serosanguinous fluid were removed from the left pleural cavity. Specimens of this fluid and of sputum were injected into mice, all of which survived. Following the thoracentesis the physical signs indicated the presence of consolidation of the lower lobe of the left lung. Streptomycin 0.5 gm. daily in divided doses was continued for a total of 11 days because of the persistence of slight fever. At the time of discharge from the hospital there was still a moderate amount of fluid in the left pleural cavity. The spleen was no longer palpable. The serum agglutination titer had risen to 1:40,960. Two months later he was well and at work. A roentgenographic examination of the chest revealed only residual pleural thickening.

Case 3. (*Figure 3*) *J. E. Ulceroglandular tularemia; bronchopneumonia; encephalitis.* This 67 year old white farmer dressed a wild rabbit nine days before the appearance of an ulcer on the right thumb and the development of chill, high fever and severe headache. Within 24 hours he had pleural pain and a nonproductive

cough. He was admitted to the St. Thomas Hospital on the service of Dr. B. H. Webster on the sixth day of illness in a semistuporous state.

When aroused he complained bitterly of headache. An indurated ulcer was present on the left thumb and the left epitrochlear and axillary lymph nodes were large and tender. Many fine moist râles were heard over both lung fields and a roentgenogram revealed diffuse bilateral bronchopneumonia. The leukocyte count was 10,600.

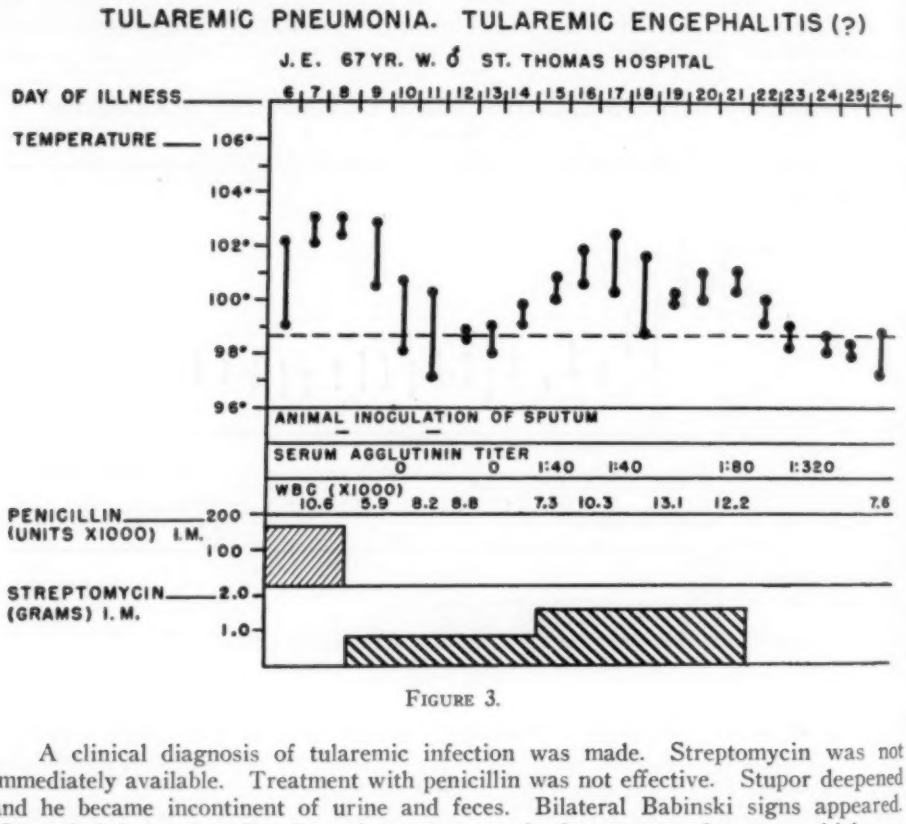

FIGURE 3.

A clinical diagnosis of tularemic infection was made. Streptomycin was not immediately available. Treatment with penicillin was not effective. Stupor deepened and he became incontinent of urine and feces. Bilateral Babinski signs appeared. No agglutinins against *P. tularensis* were present in the serum, and sputum which was injected into mice failed to produce tularemic infection. Streptomycin treatment was begun on the third hospital day in doses of 0.8 gm. daily, intramuscularly in divided doses at four-hour intervals. The temperature gradually fell to normal in a period of five days, clearing of the pneumonia was demonstrated by roentgen-ray examination and the ulcer and lymphadenopathy exhibited improvement. However, stupor continued and the temperature again rose. On the fourteenth day of illness (ninth hospital day) the cerebrospinal fluid was found to be under normal pressure and contained 20 mg. of protein. The cell count was 29 per cu. mm. and the majority of cells were granulocytes. The dose of streptomycin was increased to 1.6 gm. per day. Within 48 hours the patient exhibited marked improvement. He became mentally alert and was free of headache. Serum agglutinins against *P. tularensis* were demonstrated for the first time on the fifteenth day of illness. Streptomycin was continued for a total of two weeks' treatment. The temperature gradually fell to normal values. The Babinski signs disappeared. The serum agglutinin titer rose

to 1:320. On the twenty-third day of illness a second cerebrospinal fluid examination revealed 2 leukocytes per cu. mm. The protein content was 60 mg. per 100 c.c. The patient was seen six weeks following his discharge from the hospital. He was in good health. The serum agglutinin titer was 1:320.

Comment: The failure to recover *P. tularensis* from the sputum by mouse inoculation is attributed to faulty technic in the collection of the specimen. The appearance of agglutinins in the serum and the response of the ulceroglandular and pulmonary lesions to streptomycin confirmed the clinical diagnosis of tularemic infection. The nature of the cerebral complication was not clear. The clinical picture and the improvement following larger doses of streptomycin suggest that tularemic lesions were present in the brain.

Tularemic Infection in the Absence of Ulceroglandular Lesions

(Cryptogenic infection)

As indicated above the recognition of tularemic infection, with or without pulmonary involvement, poses no problem when the typical primary ulcer and regional buboes are present. In the absence of these tell-tale lesions the clinical picture is obscure and etiologic diagnosis must attend upon either the demonstration of the organism by culture or animal inoculations, or the development of specific agglutinins in the blood serum. The former diagnostic procedure is dangerous and time-consuming. Specific agglutinins do not appear until the end of the second or during the third week of tularemic infection. Thus, patients with severe tularemic infections may die before an accurate etiologic diagnosis can be established by these laboratory methods.

The incidence of pleuropulmonary tularemia in the absence of ulceroglandular lesions is indicated by table 2. Over half of the Vanderbilt and

Table II

Incidence of Ulceroglandular Lesions in Pleuropulmonary Tularemia
(V.U. Hospital and Vet. Ad. Hospitals)

Ulceroglandular Lesions	Number	Per Cent
Absent	16	59
Present	11	41
Total	27	100

Veterans Administration patients had no ulceroglandular lesions and presented themselves with pleuropulmonary infections of unknown etiology. Thus, primary atypical pneumonia of unknown etiology, viral pneumonia of known etiology (influenza, psittacosis, lymphogranuloma venereum, lymphocytic choreomeningitis) and tuberculous infection were considered originally as diagnostic possibilities.

Cases 4, 5, and 6 are examples of pleuropulmonary infection due to *P. tularensis* which, since they occurred in the absence of the classical ulceroglandular lesions, constituted difficult diagnostic problems.

Case 4. (*Figure 4*) *H. H. Tularemic pneumonia; pleural effusion.* This 37 year old business man developed high fever, pleural pain and prostration 10 days before admission to the Vanderbilt University Hospital. Sulfathiazole treatment for pneumonia was administered without benefit for six days. Then sulfathiazole was replaced by sulfadiazine and penicillin was begun. Four days before admission to the hospital a pleural friction rub and fine moist râles were heard over the right lung and he seemed much worse.

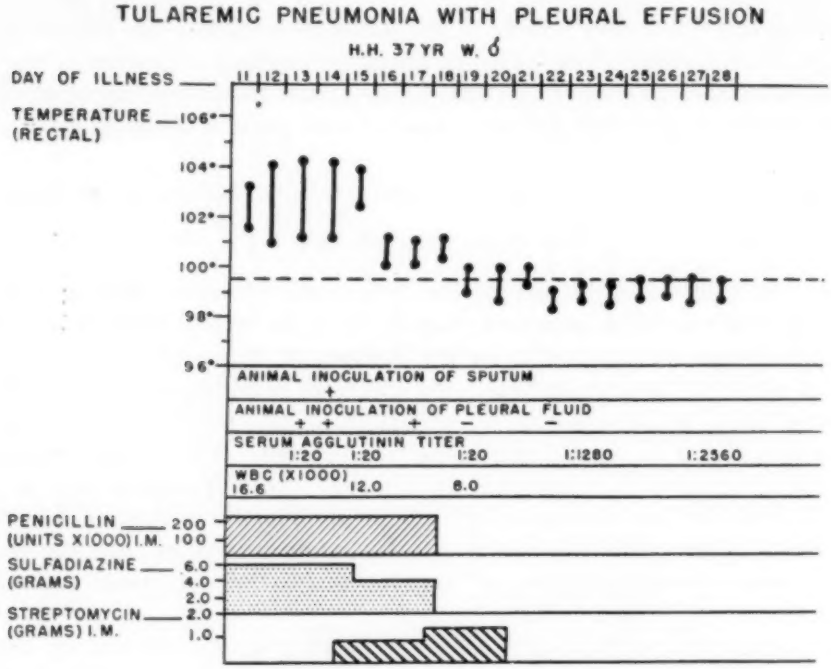

FIGURE 4.

On admission to the hospital he appeared desperately ill. High fever was present and he was dyspneic and cyanotic. The skin and superficial lymph nodes were normal. The physical signs of pneumonia and left pleural effusion were confirmed by roentgen-ray examination. The area of consolidation was in the hilar region. The leukocyte count was 16,600. Microscopic examinations of the sputum revealed few organisms of any kind. A tentative diagnosis of severe primary atypical pneumonia was made and treatment with penicillin and sulfadiazine was continued. Thoracentesis yielded 60 c.c. of sanguinous fluid containing 12,000 leukocytes per cu. mm. Cultures of this fluid by routine methods produced no growth. On the fourteenth day of illness he became stuporous. A second thoracentesis yielded 450 c.c. of dark bloody fluid. The possibility of cryptogenic tularemic infection was considered. Members of the family stated that there had been no exposure to wild rodents. It was recalled that he had removed ticks from his dog on several occasions prior to the development of the present illness. A therapeutic trial with streptomycin was decided upon. Before the administration of streptomycin specimens of sputum and pleural fluid were injected into mice. All of the mice died and *P. tularensis* was cultured from their spleens. An agglutination titer of the patient's serum against *P. tularensis* of 1:20 was reported.

On the fourteenth day of illness streptomycin treatment was begun, 0.8 gm. daily, intramuscularly in divided doses at four hour intervals. The following day the temperature was somewhat lower and the patient's mental state was clearer. Forty-eight hours later marked improvement was noted. There was much less dyspnea and cyanosis. On the third day of streptomycin treatment the dose was increased to 1.6 gm. Four hundred and fifty c.c. of pleural fluid were aspirated. Specimens were injected into mice which again yielded *P. tularensis*. Nevertheless, the patient improved steadily and streptomycin treatment was terminated after seven days. Specimens of pleural fluid obtained after the fifth day of streptomycin treatment failed to infect mice. The serum agglutinin titer rose from 1 : 20 to 1 : 2560. When seen one month after his discharge from the hospital the patient felt well. Fluoroscopic examination of the chest showed residual pleural thickening.

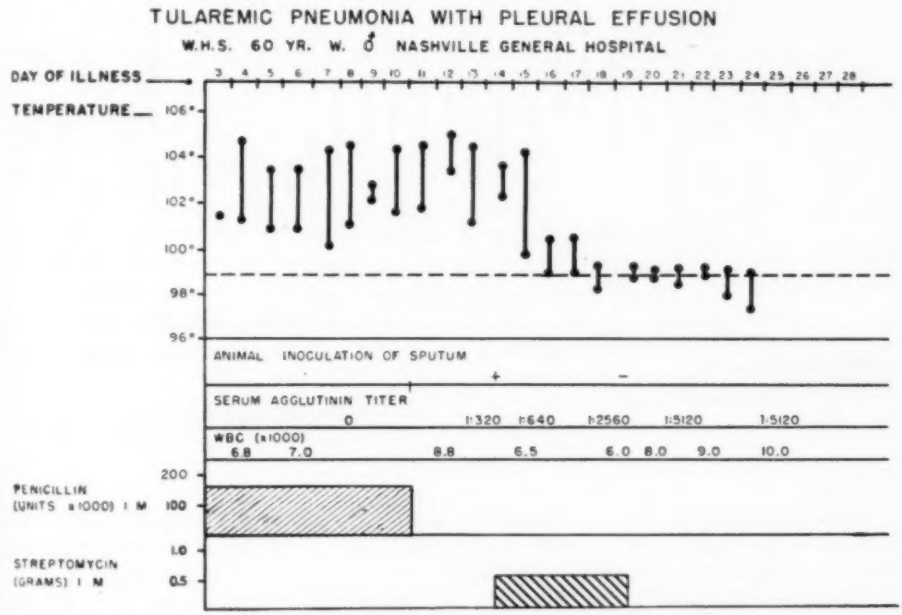

FIGURE 5.

Case 5. (*Figure 5*) *W. H. S. Tularemic pneumonia with pleural effusion.* Two days before admission to the Nashville General Hospital this 60 year old farmer experienced a shaking chill associated with fever and prostration. He soon became delirious. On admission to the hospital he was semi-stuporous. The skin was normal and there was no enlargement of the superficial lymph nodes. Two small shallow dirty ulcers were present on the pharyngeal pillars. Physical signs over the lower lobe of the right lung indicated an area of consolidation and roentgen-ray examination confirmed the presence of bronchopneumonia. The spleen was not palpable. The leukocyte count was 6800. Penicillin treatment was instituted without effect upon the illness. He continued to have high fever and stupor deepened. On the seventh day of the illness diarrhea developed and persisted during the following week. The presence of a small pleural effusion was noted. Serum agglutinins against *P. tularensis* were absent on the eighth day of the illness but were present on the fourteenth day 1 : 320. Sputum obtained at this time yielded *P. tularensis* on mouse inoculation. Streptomycin 0.6 gm. daily in divided doses intramuscularly at four hour intervals

was begun. Within 24 hours he became rational and alert. The diarrhea ceased. The temperature fell abruptly to lower values and within four days became normal. The pharyngeal ulcers healed. Prior to and during the period of streptomycin therapy the amount of fluid in the right pleural cavity slowly increased and on the day the antibiotic was discontinued 1000 c.c. of serosanguinous fluid were removed. Specimens of this fluid failed to produce infection when injected into mice. The fluid did not reaccumulate and the patient was discharged from the hospital, apparently well.

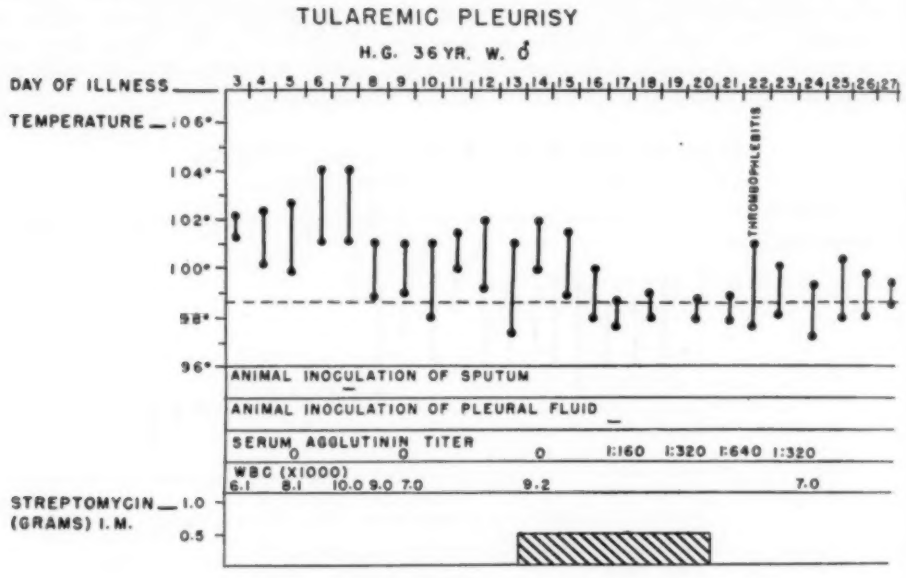

FIGURE 6.

Case 6 (*Figure 6*) *H. G. Acute tularemic pleurisy.* A 36 year old farmer was admitted to the Vanderbilt Hospital on the third day of an acute illness initiated by chill, fever, and epigastric pain. The latter was aggravated by coughing.

He appeared acutely ill. The skin and superficial lymph nodes were normal. The lungs were clear. There was marked epigastric tenderness and voluntary muscle spasm. The spleen was felt one finger's breadth below the costal margin. The leukocyte count was 6100. A roentgen-ray examination of the chest revealed no abnormalities.

During the first week of hospitalization the patient had high remittent fever. A pleural friction rub developed over the left chest and on the seventh day of illness there were signs suggestive of a left pleural effusion. A thoracentesis yielded no fluid. A pneumothorax, induced at the time of the thoracentesis, relieved the pleuritic pain. The possibility of tularemic infection was considered. The patient denied contact with wild rodents but during his work as a woodcutter he had repeatedly removed ticks from his skin. No serum agglutinins against *P. tularensis* were present on the fifth, ninth and fourteenth days of illness. Nevertheless, on the fourteenth day, streptomycin treatment was begun as a therapeutic trial. One-half gm. daily was administered in divided doses at four hour intervals. In 24 hours malaise had disappeared and he said that he felt perfectly well. Within four days the temperature became normal. On the third day of streptomycin therapy (sixteenth day of illness) 8 c.c. of straw-colored fluid were aspirated from the left pleural cavity and injected into

mice. All survived. The following day agglutinins against *P. tularensis* were demonstrated in the serum for the first time, in a dilution of 1 : 160. During the next week there was a progressive rise in the titer to 1 : 640. The pleural effusion gradually disappeared. Convalescence was complicated by the development of left femoral thrombophlebitis. Recovery was complete.

Comment: It seems highly probable that patients H. H. and H. G. (Cases 4 and 6) were infected with *P. tularensis* as a result of contacts with ticks. Patient W. H. S. (Case 5) may represent infection by the oral route, the ulcers of the pharyngeal mucous membrane constituting the primary lesions. However this may be, the nature of the infection was obscure in each instance and as a result specific, curative treatment was delayed. Patients H. H. and H. G. were desperately ill. It is entirely possible that further delay in the administration of specific therapy would have proved fatal.

The extraordinary effectiveness of streptomycin in the treatment of tularemic infections is indicated in the combined experience of the Vanderbilt Hospital and the Veterans Administration Hospitals. Twenty-seven patients with tularemic pleuropulmonary infection were treated. Only one death occurred and this is believed to have resulted from pulmonary artery embolism during convalescence from the pulmonary infection.

TABLE III

Pleuropulmonary Tularemia Treated with Streptomycin

	Number	Recovery	Death
Vanderbilt University Hospital	12	11	1
Veterans' Administration Hospitals	15	15	0
Total	27	26	1

SUMMARY

More than one-fourth of the tularemic infections observed in Veterans Administration Hospitals during a nine month period in 1946 had pleuropulmonary involvement.

Only 40 per cent of patients in the Vanderbilt and Veterans hospitals group with pleuropulmonary tularemic infection had tell-tale ulceroglandular lesions. Thus, more than half presented themselves as obscure pulmonary infections or masqueraded as primary atypical pneumonia of unknown etiology. Under such circumstances, even when the possibility of tularemic infection is considered and diagnostic tests for its presence are employed, the clinician is seriously handicapped, for the demonstration of *P. tularensis* in culture or by mouse inoculation is time consuming and dangerous, and diagnostic agglutinins do not appear in the patient's blood until the end of the second or during the third week of infection.

Streptomycin is curative in pleuropulmonary tularemia, the pre-streptomycin mortality of which was from 20 to 40 per cent. In suspect cases

a therapeutic trial with streptomycin, as recommended by Hunt, may save life in an infection which sometimes kills before the appearance of serum agglutinins and before culture or mouse inoculation yields the causative organism. Administration of streptomycin does not inhibit the subsequent appearance of diagnostic agglutinins. Therefore, a therapeutic trial with streptomycin is indicated in critically ill individuals suspected of having severe primary atypical pneumonia or other forms of viral pneumonia, when the illness is of less than two weeks' duration and when it occurs in a region where tularemia is endemic.

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NITROGEN MUSTARD AS A THERAPEUTIC AGENT FOR HODGKIN'S DISEASE, LYMPHOSARCOMA AND LEUKEMIA *

By MAXWELL M. WINTROBE, F.A.C.P., CHARLES M. HUGULEY, JR.,†
MARGARET T. MCLENNAN and LUCIO PENNA DE CARVALHO
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THE nitrogen mustards differ from the mustard war gas only in that nitrogen replaces sulfur. Study of the biological effects of the nitrogen mustards has revealed that they parallel and are almost identical with the biological effects of radiant energy.

The most important properties of the beta chloroethyl amines (nitrogen mustards) are outlined in table 1. While these substances are stable and

TABLE I

Properties of β-Chloroethyl Amines (Nitrogen Mustards)

Contact vesicants. *Also* cytotoxic following absorption.
Physiological activity due to the intramolecular cyclization of the compound in a polar solvent to form a cyclic onium cation.
Pronounced nucleotoxic action. Inhibits mitosis. Induces chromosomal abnormalities.
Severity of response directly related to dose used.
Susceptibility of cells related to degree of proliferative activity.
Lymphatic tissue, bone marrow and mucosa of gastrointestinal tract especially susceptible. In large enough doses all cells are affected.
So reactive that effects are over in less than five minutes.
Manner of action possibly related to action on an enzyme system.

unreactive in dry form, in aqueous solution a rapid change takes place. The beta carbon forms a ring with the nitrogen to make a quaternary ammonium base, with the release of chloride ion. The quaternary ammonium ion is highly active and reacts with a variety of biologically important chemical groupings such as amino, carboxyl, sulfhydryl, etc. The intravenous administration of these compounds was found, as the result of investigation carried out during the second world war, to produce almost complete dissolution of lymphoid tissue in 24 hours.[1] The bone marrow is also affected, particularly the granulocytes. With sufficient dosage complete aplasia can be produced. In addition, degenerative changes in the epithelial tissue of the gastrointestinal tract can be produced if very large doses are given, and

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‡ On leave from the University of Sao Paulo, Sao Paulo, Brazil.

even a hemorrhagic enteritis can ensue. If the amount given is great enough, every cell in the body can be affected. These compounds are so reactive that their effects are over within a few minutes. It was observed, for example, that occlusion of circulation to a given area for five minutes afforded complete protection of that area.

The susceptibility of cells to the action of these compounds is related to the proliferative activity of the cells. The effects are similar to those of radiant energy. Mitotic activity is inhibited and chromosomal abnormalities can be induced. The first trial of the nitrogen mustards for the treatment of neoplasms involving the lymphoid and hemopoietic tissues was reported by Gilman, Goodman, Lindskog and Dougherty.[2] Preliminary reports of investigations at the University of Chicago,[3] the University of Utah[4] and elsewhere[5] have now appeared.

Material and Methods

To date we have used nitrogen mustard in the treatment of 77 cases of Hodgkin's disease, lymphosarcoma, leukemia and certain miscellaneous disorders. In all of these cases the hydrochloride salt of di(β-chloroethyl) methyl amine ($CH_3N(C_2H_4Cl)_2$) was used. The following method of administration has been found to be the most satisfactory. A saline infusion is started and its smooth running into the vein assured. Then to 10 milligrams of the dry white crystalline hydrochloride salt of the mustard, obtainable in small sterile bottles, 10 c.c. of sterile physiologic saline are added. The salt dissolves promptly and the calculated dose of solution is withdrawn into a sterile syringe. This is immediately administered to the patient by injecting it through the rubber tubing of the saline infusion. Care is taken to avoid touching the skin or mucous membranes of the patient or physician with any of the solution although no harm has resulted from accidental spilling when the skin has been washed immediately. It is important that the nitrogen mustard be injected promptly after it has been dissolved as its activity is quickly dissipated. The injection of the concentrated salt through the tubing of the saline infusion allows it to be washed into the veins quickly. The concentrated solution injected into a vein may produce phlebothrombosis, and extravasation into the surrounding tissue can produce necrosis and sloughing.

The dosage used has usually been 0.1 milligram per kilogram body weight. As a rule four to six infusions have been given at intervals of one or two days depending on the presence or absence of severe toxic symptoms. In several cases as many as eight daily infusions have been given and in one patient as much as 0.25 milligram has been given per kilogram body weight per dose. In a few cases, smaller doses have been used. In patients with chronic leukemia or Hodgkin's disease who had already responded to nitrogen mustard therapy, maintenance therapy has been carried

out by giving two or three infusions on successive days at two to four week intervals. This has been done without hospitalizing the patients.

Clinical Results

In table 2 statistical data concerning the cases treated are presented and in table 3 the results of treatment are summarized. The designation, "good" response, has been used if a patient was able to return to his usual occupation for several months or more and was free of troublesome symptoms.

Table II

Statistical Data Concerning Patients Treated with Nitrogen Mustard

Diagnosis	Total No. of Cases	Sex		Age		Duration of Symptoms before Admission		Number Previously Treated with X-ray
		M	F	Range Yrs.	Av. Yrs.	Range Mos.	Av. Mos.	
Hodgkin's disease	28	16	11	14–67	36.3	3–60	23.8	22
Lymphosarcoma	11	6	5	11–82	49.5	1–60	16.4	5
Leukemia ch. myel.	8	4	4	28–58	43	3–48	29.0	5
Leukemia ch. lymph.	10	8	2	45–87	59	1–132	37.0	4
Leukemia acute	8	4	4	2–65	21	6–120 days	52 days	0
Misc.*	12	9	4	22–75	46	1–84	22.6	5

* Presumptive but unproved Hodgkin's disease 2, metastatic carcinoma 4, multiple myeloma 2, malignant melanoma 1, carcinoma bronchus 1, Kaposi's sarcoma 1, fibrosarcoma (metastatic) 1.

Table III

Results of Treatment with Nitrogen Mustard, 65 Cases

Diagnosis	Total No. of Cases	Nitrogen Mustard		Results			Patients Living		Patients Dead	
		No. of Doses	Total Dosage Mg.	Good	Fair	Poor	No.	Time since 1st Treat. Mos.	No.	Time from Rx to Death Mos.
				Per Cent						
Hodgkin's disease	28	4–40	24–193	61	18	21	15	1–26	12	¼–16
Lymphosarcoma	11	1–20	4–120	36	—	64	2	2–5	9	1.5–12
Leukemia, ch. myel.	8*	2–41	12–294	43	14	43	6	1–22	2	1–3
ch. lymph.	10	1–10	7–87	30	10	60	6	1–24	3	3–30 d.
acute	8	3–22	4–64	—	38	62	0		8	0.5–3.5

* Includes one case with inadequate follow-up.

If there was definite improvement but of a less striking or more short-lived nature the response is termed "fair." In this category have also been placed cases in which striking relief of some particularly distressing symptom such as intractable pain occurred even though the course of the illness was not significantly altered otherwise. Those cases which have shown little if any improvement or in which the improvement lasted for only a few weeks are classified as "poor" responses.

In the cases which have been studied almost all stages and manifestations of the diseases under consideration have been represented. Consequently, it is difficult to offer a final evaluation of results. The comments which will be made must be understood to be of a preliminary character and as offering simply a running account of experience to date.

Hodgkin's Disease. In this series of 28 patients, one of the most constant and striking effects of nitrogen mustard was upon fever in those patients who manifested this sign of the disease. With the exception of one case of Hodgkin's sarcoma and one terminal case with secondary infection, the first course of nitrogen mustard caused the temperature to return to normal, and in many patients this effect was repeated many times in subsequent courses. In most cases, along with the beneficial effects upon the fever, there was an increased feeling of well being, improvement in appetite, gain in weight and general clinical improvement. In some patients, the upsurge in appetite following therapy was one of the most striking effects noted. The duration of remissions varied from a few days to several months.

In general, large lymph nodes decreased moderately in size following treatment with nitrogen mustard. In those patients who had enlargement of the spleen, a reduction in the size of this organ usually followed nitrogen mustard therapy. In 19 of our patients with Hodgkin's disease, there was evidence of mediastinal lymph node enlargement or lung parenchyma involvement. In a number of these patients a clear-cut effect on mediastinal widening, extent of parenchymal change, dyspnea and, particularly, on the associated hacking cough was noted. Even dysphagia associated with the presence of a mediastinal mass has been relieved.

The influence of nitrogen mustard on pruritus has varied depending, it seems, on whether or not nitrogen mustard proved effective in the treatment of the disease as a whole. In three patients, back pain constituted one of the most distressing symptoms of the disease. In two of these roentgenographic evidence of bone involvement was present. All three patients obtained dramatic relief following nitrogen mustard therapy. In two patients abdominal pain was relieved following nitrogen mustard therapy.

Nine patients in this series were extremely ill and were responding no longer to roentgen-ray therapy. One of the most striking beneficial effects of nitrogen mustard therapy which we have observed to date has been the remarkable improvement which has occurred in five of these "roentgen-ray resistant" patients (figure 1).

Of the 28 patients with Hodgkin's disease, 15 are living at the present time and 13 are dead. In six patients (21 per cent) the results were definitely poor. In 17 (61 per cent) they may be classified as good, while in 5 (18 per cent) the response could be characterized as only fair. The responses thus have varied greatly and a noteworthy feature is the fact that it seems to be difficult to estimate in advance whether a response will be good

or poor. As already mentioned, several patients who seemed nearly terminal responded surprisingly well. Others, however, even early in the disease showed only a brief response to nitrogen mustard therapy. The remissions in our cases have varied greatly in duration. The longest has been 27 months and the shortest was three weeks.

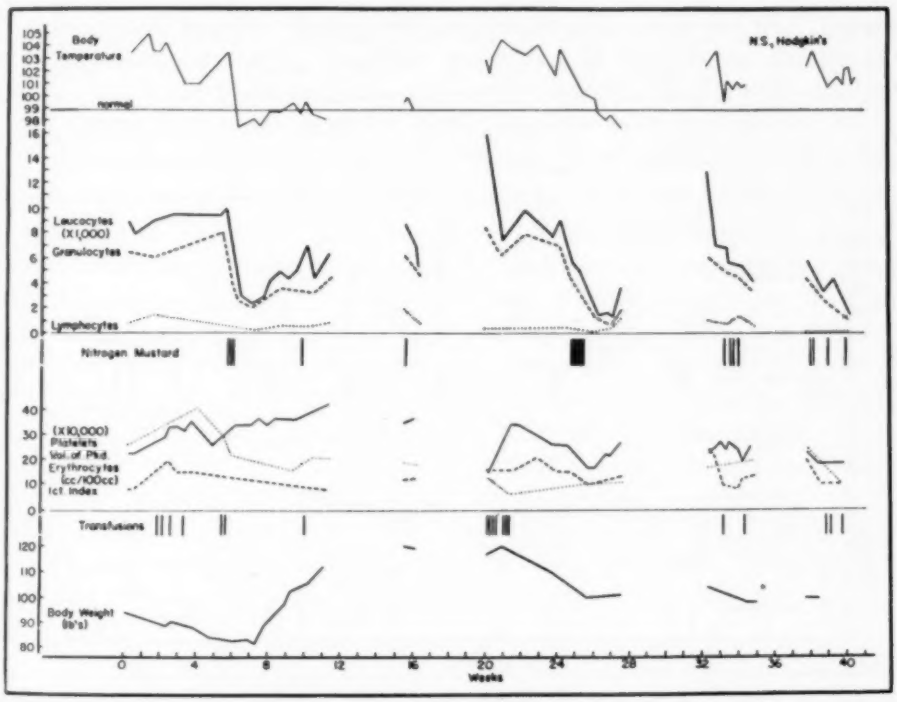

FIG. 1. Course of a patient with severe anemia somewhat hemolytic in type, associated with Hodgkin's disease who seemed in a terminal stage after treatment with roentgen irradiation and Fowler's solution. With blood transfusions as well as nitrogen mustard fever disappeared, the anemia was relieved and weight was gained. Several other remissions were produced in this patient but each was successively less striking and of shorter duration.

Lymphosarcoma. In this group of 11 cases great individual variation in response to nitrogen mustard therapy has been observed. The response has ranged from a remarkable melting away of tumor masses following treatment with long remission, to essentially no benefit whatever. In roentgen-ray resistant cases, no dramatic benefit has been observed like that seen in some cases of Hodgkin's disease.

Leukemias. Of the eight patients with *chronic myelocytic leukemia* treated with nitrogen mustard one was terminal on admission and resistant to roentgen-ray therapy. In this case nothing was achieved with nitrogen mustard therapy. Of the remaining seven patients good results have been obtained in three, fair results in one, and poor results in two, both of whom died after three months of therapy. One patient did not complete her

course of therapy. In several cases, it has been possible to produce remissions a number of different times by giving courses of three to five infusions of nitrogen mustard at two to four month intervals (figure 2). Where a favorable response to therapy has been achieved there has not only been a reduction in the white cell count to normal but the platelet count has returned to normal when it was above or below normal and anemia has been relieved. At the same time the spleen was greatly reduced in size, weight was gained, and a sense of well being returned. Thus the effect has been similar to that which is observed following roentgen-ray therapy. By giving two or three infusions on successive days at two to six week intervals it has been possible to maintain two patients in a satisfactory state of health.

FIG. 2. Course of a case of chronic myelocytic leukemia under nitrogen mustard therapy. Note the drop in leukocyte count, disappearance of anemia, and gain in weight. This patient is now receiving treatment with two infusions of nitrogen mustard at intervals of two to four weeks as illustrated at the right-hand portion of the chart, and is responding very satisfactorily.

Of the 10 patients with *chronic lymphocytic leukemia* three patients are in remission nine to 26 months after therapy was first given. The cases of chronic lymphocytic leukemia seem to fall into one of two groups: (1) those patients who were really not ill and in whom the characteristic blood findings were more or less incidental; and (2) the cases of long standing with marked lymphadenopathy, splenomegaly, thrombocytopenia and severe anemia. The first group responded favorably to nitrogen mustard therapy and have had long remissions following treatment. The patients of the second group were refractory to the agent and responded not at all or only slightly after its administration (figure 3).

Eight patients with *acute* or *subacute forms of leukemia* have been treated and of these five must be classed as "poor" results and three as "fair" results. In two patients there was temporary improvement sufficient to enable the

patient to leave the hospital. In a third patient the acute course of the disease seemed to have been altered and at first there was some clinical improvement. Ultimately the patient failed to respond to further therapy, as was the case in all the rest. A gratifying result of treatment in two patients was the relief of severe bone pain which could be achieved even with extremely small doses of nitrogen (0.04 mg. per kg. body weight).

Uncertain Diagnoses and Miscellaneous Disorders. No alteration in the downward course of these patients was observed except possibly in two cases. One was a patient who had metastatic carcinoma of the mediastinal lymph nodes presumably from a uterine carcinoma. She suffered from chest pain and dyspnea and was temporarily relieved of these symptoms after nitrogen mustard therapy. Again, in a patient with metastatic anaplastic carcinoma of the chest wall and breast a remarkable regression of the metastatic nodules and reduction in jaundice followed nitrogen mustard therapy.

Hematological Effects. The most consistent effect of nitrogen mustard on the blood was a reduction in the total leukocyte count. This was reduced in all cases and the effect of the therapeutic agent was expressed not only in a fall in lymphocytes but also in granulocytes (figure 4). Varying with the magnitude of the initial white cell count, the level dropped to normal or leukopenic levels and in one patient dropped as low as 200 cells per cubic millimeter. Only in one case, however, did the clinical picture of agranulocytosis appear with sore throat and fever. The prompt administration of penicillin was effective in relieving the infection. In several instances the concurrent administration of this agent probably prevented the development of infection.

In general, the effect of nitrogen mustard on the blood was biphasic. There was frequently (1) an initial depression of leukocytes, and sometimes of platelets and red cells or a further drop from a previously existent low level, toward the end of the second week following therapy. Whether or not this occurred there was (2) a later therapeutic effect which corresponded usually with the degree of general improvement of the patient. The leukocyte count returned to normal, as did the platelets, and the anemia disappeared. This was noted not only in cases of chronic leukemia, as already mentioned, but was also seen in patients with Hodgkin's disease, some of whom had severe anemia prior to therapy. The length of time that the leukocyte count remained low following therapy depended to some extent on the severity of the leukopenia, but recovery usually began within a week.

There seemed to be no definite correlation in any of our cases between the degree of fall in red cell level and the size of the dose administered. It seemed that in the dosage used nitrogen mustard rarely produced anemia in cases of Hodgkin's disease and lymphosarcoma. An increase of anemia following therapy could as readily be attributed to the effect of the underlying disease as to the chemotherapeutic agent employed.

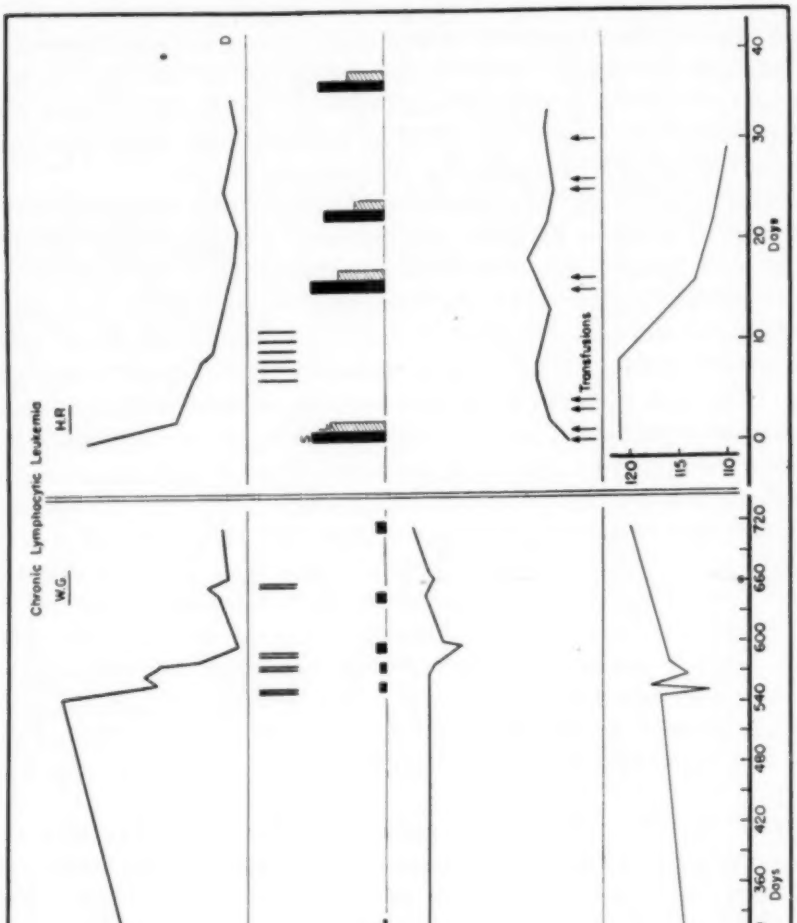

FIG. 3. Course of two cases of chronic lymphocytic leukemia under nitrogen mustard therapy. In W. G. (Case 1) the general condition was good from the beginning and only a slight increase in the sense of well-being was observed following therapy. In H. R. (Case 6) the general condition was poor and treatment produced no significant improvement.

Although thrombocytopenia was produced in a number of the patients (26 out of 77), petechiae appeared only in seven and, with the exception of one patient who died of lymphosarcoma, these cleared as the platelet count rose. There was never any serious bleeding in any of the cases.

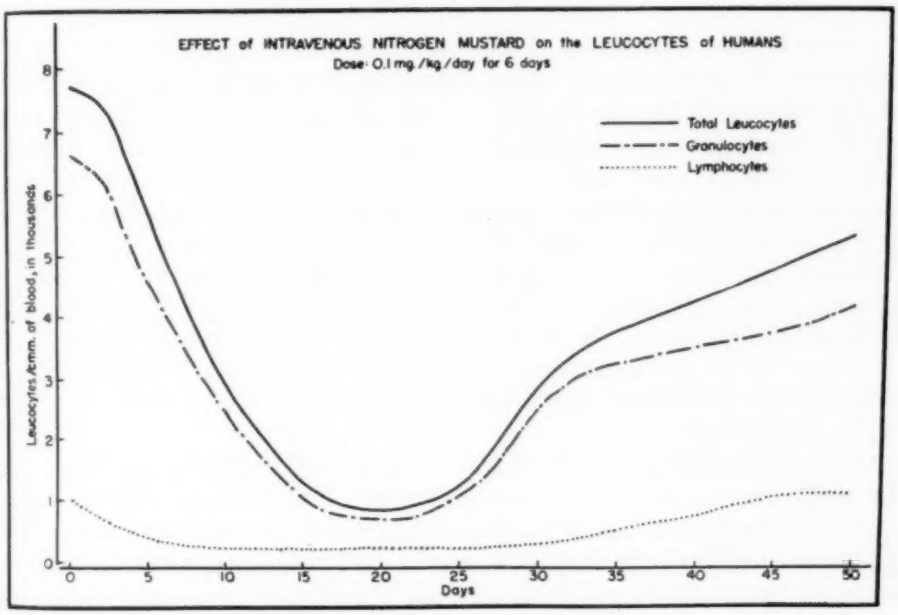

FIG. 4. Schematic diagram of effect of nitrogen mustard on the leukocytes.

Toxic Effects. Some degree of nausea and vomiting occurred in nearly every patient given nitrogen mustard. The gastrointestinal symptoms varied, however, from simple anorexia to severe nausea with repeated vomiting, in a few patients. These symptoms appeared within three hours after the injection of the drug and were of varying duration but rarely lasted more than a few hours. The first one or two infusions in a course of therapy usually produced more nausea than subsequent infusions. Many patients were relieved of the discomfort by preinfusion administration of a sedative. A satisfactory method of management is to give the patient a sedative in the early evening and to administer nitrogen mustard about 7:00 or 8:00 p.m. Thus, any nausea or vomiting which may be produced occurs at night and if the patient is sufficiently sedated he is not greatly disturbed. By this means food intake has not been interrupted to any great extent. A number of patients have expressed their preference for this time and mode of administration.

In only one patient was a significant degree of damage to the veins produced and this occurred prior to the introduction of the method of administration in the course of an intravenous saline infusion which has been

described already. Additional toxic effects which have been mentioned already are the severe leukopenia which can be produced by nitrogen mustard therapy and thrombocytopenia.

Discussion

An adequate evaluation of the usefulness of nitrogen mustard in the treatment of the conditions under discussion here would require the study of a much larger number of cases in each category, and observation for a longer period of time than has been possible so far. It seems clear, however, that nitrogen mustard therapy is comparable in its effect to that produced by adequate doses of roentgen therapy. Whether nitrogen mustard is more or less effective than roentgen therapy in Hodgkin's disease is difficult to state but one cannot help being impressed by the fact that in a number of patients who had apparently become resistant to roentgen therapy, substantial benefit followed the introduction of nitrogen mustard therapy.

There is no evidence from our cases that nitrogen mustard therapy possesses any advantage as compared with roentgen therapy in the treatment of lymphosarcoma.

A beneficial effect in cases of chronic myelocytic leukemia has been quite clear in a number of instances but again there is no evidence that this effect is greater than that achieved with roentgen therapy. The same can be said regarding chronic lymphocytic leukemia. The temporary remissions observed in two cases of acute leukemia and the relief of bone pain in this disease have been mentioned already.

Nitrogen mustard therapy offers the advantages of ease of administration and availability under conditions where roentgen therapy may not be obtainable. It must also be noted that the tolerance of patients with the disease under discussion to various therapeutic agents varies greatly. The availability of nitrogen mustard in addition to roentgen therapy offers another therapeutic tool. The effectiveness of nitrogen mustard in some cases of Hodgkin's disease which had become resistant to roentgen-ray therapy is a very important consideration. An important feature relating to the introduction of nitrogen mustards as therapeutic agents depends on the fact that the one employed in this study is but one of a series of compounds of almost infinite number. It can be hoped that, by changing substituent groups, the reactivity, toxicity and other important properties of the nitrogen mustards can be so altered that a much more valuable therapeutic agent than di(β-chloroethyl) methyl amine hydrochloride can be discovered. The most important objection to nitrogen mustard is the fact that it is a potent hemopoietic toxin and that the margin of safety between the therapeutic dose and the serious toxic dose is narrow. Frequent careful hematologic examinations are, therefore, mandatory. In experienced hands, however, the agent is very useful and its use is associated with little danger.

Unfortunately, the response to nitrogen mustard in various patients seems to be largely unpredictable and consequently a therapeutic trial must, in the last analysis, give the answer as to whether this agent is likely to be beneficial or not.

Summary

1. The effects of di(β-chloroethyl) methyl amine hydrochloride (nitrogen mustard) in 77 patients, 28 with Hodgkin's disease, 11 with lymphosarcoma, 26 with leukemia and 12 with miscellaneous disorders, are described.

2. A salutary effect upon lymph nodes, fever, splenomegaly and various clinical symptoms was observed in many patients with Hodgkin's disease, lymphosarcoma and leukemia.

3. In general, the effects of nitrogen mustard in these diseases were similar to those produced by roentgen irradiation.

4. Nitrogen mustard has produced remissions in several patients with Hodgkin's disease who were considered to be roentgen-ray resistant.

5. Toxic manifestations of nausea and vomiting were observed in most patients following nitrogen mustard administration but the intensity of these symptoms varied greatly and was almost insignificant in some.

6. Nitrogen mustard therapy almost invariably resulted in a decrease in leukocyte count with lymphocytopenia and granulocytopenia. This was often accompanied by a variable decrease in red cells and a decrease in platelets but in no patient did serious complications arise as a result of these effects.

7. Following the initial decrease in blood elements, an increase in red cells even with complete disappearance of anemia was the result in those patients responding favorably. Leukopenia and thrombocytopenia likewise disappeared.

8. Nitrogen mustard offers certain advantages as compared with roentgen irradiation in some cases of Hodgkin's disease and leukemia. These include the ease of administration, the effectiveness at times in patients "resistant" to roentgen-ray therapy and, very rarely, a better tolerance for nitrogen mustard than for irradiation. Ultimately, however, nitrogen mustard, like irradiation, has proved ineffective in many cases.

9. Adequate evaluation of the place of nitrogen mustard therapy in the management of "lymphomas" and leukemias must await a longer period of observation than has been possible so far and requires the study of a large number of cases. Experience to date, however, indicates that continued use is justified and a search for less toxic and more effective agents of this type is warranted.

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THE DEVELOPMENT OF BASOPHILIC INCLUSION BODIES IN MYELOMA CELLS AFTER STILBAMIDINE TREATMENT *

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IT has been reported previously that in many cases of multiple myeloma injections of stilbamidine—occasionally of pentamidine—exert a favorable influence upon the excruciating pains from which the patients so frequently suffer.[1, 2, 3, 4] From the beginning it has been emphasized that the disease is not cured by stilbamidine. Even in patients who are markedly relieved, the characteristic myeloma cells still abound in the bone marrow, and Bence Jones proteinuria and hyperglobulinemia continue unabated. At the very best the disease may be halted temporarily. In some patients the relief of pains has persisted for many months. In many cases the pains recur after a shorter or longer period, but it is often possible by means of additional injections to bring relief anew. Nevertheless the death rate among these patients is still high. In patients with Bence Jones proteinuria and renal insufficiency the drug should be dispensed with caution.

It is well known that roentgen-ray treatment may occasionally alleviate the pain. Usually after one or more series of roentgen-ray treatments the disease becomes refractory. In several instances we have observed that after a series of stilbamidine injections such refractory cases could again be influenced favorably by roentgen-ray treatment.

TABLE I

Relation between the Development of Basophilic Inclusion Bodies in Myeloma Cells under Influence of Stilbamidine Treatment and the Signs of Abnormal Protein Metabolism

	Total Myeloma Patients Treated	Basophilic Inclusion Bodies Developed in
Hyperglobulinemia	13	12
Normal serum globulin $\bar{c}$ Bence Jones proteinuria	9	5
Normal serum globulin $\bar{s}$ Bence Jones proteinuria	10	0

It has been reported that after parenteral administration of stilbamidine basophilic cytoplasmic precipitates appear in the myeloma cells.[5] In the following article evidence will be presented which indicates that these characteristic precipitates are formed most readily in those patients whose protein metabolism shows the severest disturbances. Observations are now available on 32 patients with multiple myeloma treated with stilbamidine (table 1). Thirteen of these patients had an increase in the globulin content of the serum; in 12 the inclusion bodies developed readily. The thirteenth

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patient with hyperglobulinemia received stilbamidine injections only twice weekly, later three times weekly. Nine myeloma patients treated with stilbamidine had a normal serum globulin but showed marked Bence Jones proteinuria; in five of these patients basophilic inclusion bodies developed. Ten patients had neither increased globulin nor Bence Jones proteinuria. In none of these 10 patients could inclusion bodies be found, even after prolonged treatment.

TABLE II

Development of Basophilic Inclusion Bodies in Myeloma Cells under Influence of Stilbamidine Relationship with Globulin Content of the Serum

Name		Glob.	Formol gel	Bence Jones	Injections Daily		Injections Every Other Day		Total Dosage in Mg.	Inclusion Bodies
					Amt. Given in Mg.	Days	Amt. Given in Mg.	Days		
1.	Hil.	9.8	++++	−	1300	10	−	−	1300	Positive
2.	Low.	6.9	++++	−	1400	10	−	−	1400	Positive
3.	Mor.	5.6	++++	+	2025	13	−	−	2025	Positive
4.	Gersh.	3.0	++++	−	1975	16	−	−	1975	Positive
5.	Robin.	4.2	++++	−	1350	8	1050	13	2400	Positive
I.	Stern.	2.6	+	+	3150	23	−	−	3150	Positive
II.	Zapet.	1.6	−	++	2100	19	−	−	2100	Positive
III.	Bor.	1.5–3.2	− to +	++	600	7	1650	20	2250	Positive
IV.	Ros.	2.2	−	++	2250	18	−	−	2250	Positive
V.	Less.	*	−	+						Positive
VI.	Stee.	1.6	−	++	2050	19	450	5	2500	Negative
VII.	Eng.	2.1	−	++	1825	18	225	3	2050	Negative
VIII.	Lipk.	2.2	−	++	3050	21	−	−	3050	Negative
IX.	Perl.	1.4	−	−	1800	15	750	10	2550	Negative
X.	Eis.	2.4	−	−	1350	8	2700	35	4050	Negative
XI.	Kau.	2.5–3.2	−	−	2775	19	2250	45	5025	Negative
XII.	Eps.	2.4	−	−	2700	17	1800	22	4500	Negative

* Total protein 5.9%.

The treatment with stilbamidine in these 32 cases was not completely uniform. In some instances the drug was given daily, in others every second day. In most patients the injections were given intravenously. Bone marrow punctures were sometimes performed shortly after the beginning of treatment while in other patients several weeks elapsed before a bone marrow puncture was done. However, 17 of these 32 patients were treated with comparable daily doses of stilbamidine which were injected intravenously. Table 2 shows the results obtained in this group of 17 in whom the treatment was uniform. Five of these patients had a high serum globulin; in all five the daily intravenous injection of stilbamidine gave rise to the formation of inclusion bodies. In eight patients with normal serum globulin and Bence Jones proteinuria this happened five times. In four patients who had neither hyperglobulinemia nor Bence Jones proteinuria no basophilic inclusion bodies could be found. It follows from these figures that in patients with hyper-

globulinemia the basophilic inclusion bodies develop readily. This also occurs not infrequently in patients with a normal globulin content of the serum and with Bence Jones proteinuria. Up to the present time no basophilic inclusion bodies have been found after stilbamidine treatment of myeloma patients who had normal serum globulin and no Bence Jones proteinuria. It is interesting to note that all the patients who developed inclusion bodies although the globulin content of the serum was apparently normal, were treated intensively with daily injections. In myeloma patients who have hyperglobulinemia inclusion bodies are formed rapidly even when the stilbamidine treatment is not very intensive. Thus in myeloma patients with hyperglobulinemia, with or without Bence Jones proteinuria, basophilic precipitates develop regularly in the myeloma cells during stilbamidine treatment. This occurs much less readily in patients without hyperglobulinemia and then only if Bence Jones proteinuria exists.

It has been interesting to determine the minimum time and the minimum dosage of stilbamidine necessary for the development of basophilic inclusion bodies. In order to answer this question it seemed necessary to perform frequent bone marrow punctures. For obvious reasons this was difficult. The obstacle was circumvented in a patient with multiple myeloma and hyperglobulinemia in whose peripheral blood a small percentage of myeloma cells was present. In this patient after only eight injections of 150 mg. of stilbamidine fine basophilic granules could be detected in the myeloma cells of the peripheral blood. It is difficult to study this problem in routine blood smears which contain only 1 or 2 per cent of myeloma cells because, at least in the beginning of the treatment, only a small number of these rare cells show the presence of inclusion bodies. For this purpose the white cells of the peripheral blood were concentrated in the following way:

0.2 c.c. of an oxalate mixture consisting of 1.2 per cent of ammonium oxalate and 0.8 per cent potassium oxalate were evaporated in a centrifuge tube. Two c.c. of blood are added and centrifuged for three to five minutes at the speed of 2000. This supernatant serum is discarded and the sediment is transferred to a capillary tube. This capillary tube is centrifuged for three to five minutes at a speed of 2000. After centrifugation a clearcut separation between the red blood cells and the buffy coat is obtained. Then the capillary is broken off at a distance of about one millimeter above the buffy coat. The last remnant of the serum is sucked off with a fine capillary pipette. With the same fine capillary pipette the buffy coat is collected and smeared in the usual way on one or more glass slides.

The finding of basophilic inclusion bodies in the myeloma cells of the peripheral blood after the injection of 1200 milligrams of stilbamidine was confirmed by sternal punctures. In three other patients (Nos. 1, 2, and 3 of table 1) most of the myeloma cells of the bone marrow showed the

presence of basophilic inclusions after the injection of 1300, 1400, and 2025 milligrams of stilbamidine respectively.

Another point of interest is the question how long these inclusion bodies can persist after treatment has been stopped. It has become apparent that the inclusions can be found even if no stilbamidine has been given for many months. In one patient we observed that many of the myeloma cells still contained a considerable number of large inclusion bodies seven months after the injections had been terminated. In two other cases the interval between the last stilbamidine injection and the finding of inclusion bodies amounted to three and a half months and four months respectively.

Discussion

Since 1939 it has been known that stilbamidine has a specific curative influence in kala azar. Stilbamidine was tried in multiple myeloma because the two diseases had one characteristic in common: both in kala azar and in multiple myeloma an increase of the globulin content of the blood serum occurs frequently. In advanced cases of kala azar this increase is found almost constantly; in multiple myeloma hyperglobulinemia occurs in only about 60 per cent of the cases.

The results reported in this article indicate that a connection apparently exists between the abnormal protein metabolism found in multiple myeloma (hyperglobulinemia, Bence Jones proteinuria) and the formation of characteristic basophilic inclusion bodies in the myeloma cells under the influence of stilbamidine. Histochemical analysis has demonstrated that these basophilic inclusion bodies contain a conjugation product of ribose nucleic acid[6] and stilbamidine.[7] The ribose nucleic acid is a derivative of the cytoplasmic nucleoproteins. The latter nucleoproteins consist of ribose nucleic acid conjugated with a protein, the character of which is still unknown. When stilbamidine is brought into contact with nucleoprotein in vitro, a conjugation product of stilbamidine and ribose nucleic acid precipitates out.[8] At the same time the protein component of the nucleoprotein is liberated and goes into solution. Histochemical investigation of the basophilic inclusion bodies which appear in myeloma cells after stilbamidine injections indicate that a comparable process takes place in the cytoplasm of the myeloma cells. Stilbamidine evidently reacts in vivo with the cytoplasmic nucleoproteins of the myeloma cells. This reaction leads to the formation of a conjugation product of stilbamidine and ribose nucleic acid which is visualized in the form of basophilic inclusion bodies.

Autopsies have shown that these basophilic precipitates develop exclusively in the myeloma cells and in no other marrow cells. It is therefore highly probable that stilbamidine combines much more readily with the cytoplasmic nucleoproteins of the myeloma cells than with the nucleoproteins of other cells. Certain arguments can be brought forward in favor of the contention that the cytoplasmic proteins of the myeloma cells differ significantly

from the cytoplasmic nucleoproteins of other body cells. The cytoplasmic nucleoproteins of cells play an important rôle in the protein synthesis which takes place in the cells.

Many authors have emphasized that all cells with a high concentration of cytoplasmic nucleoproteins are characterized by intense protein synthesis. This holds true for the pancreatic cells which secrete protein and for the liver cells which synthesize plasma proteins. It also holds true for cells which need protein because they multiply rapidly, such as tumor cells, cells of the basal layer of the skin, and organisms such as viruses, yeasts and bacteria.[9] The high content of nucleoprotein found in the cytoplasm of the myeloma cells has also been considered as an indication of a rapid production of globulins and of Bence Jones proteins in these cells.[10] Lately it has been reported that the character of the proteins manufactured by the cell depends upon the character of its cytoplasmic nucleoproteins.[11] The latter finding leads to the conclusion that the more the cytoplasmic nucleoproteins of certain body cells differ from the norm, the more the protein synthesis of these special cells will differ from those in the other cells. The reverse must obviously be true also. In a cell like the myeloma cell which produces abnormal proteins (abnormal globulins and Bence Jones protein) cytoplasmic nucleoproteins must be present which differ from the nucleoproteins of all other normal and abnormal body cells. This may well explain why the nucleoproteins of myeloma cells show reactions which other nucleoproteins do not show and also why stilbamidine forms visible conjugation products with the cytoplasmic nucleoproteins of the myeloma cells but not with nucleoproteins of other cells.

It is interesting to note that the formation of the inclusion bodies is more marked in those myeloma patients who have hyperglobulinemia than in those who do not. It seems reasonable to suppose that in myeloma patients who have hyperglobulinemia or Bence Jones proteinuria the protein metabolism of the myeloma cells will be more abnormal than in myeloma patients with normal serum globulins and without Bence Jones proteinuria. In the former patients more abnormal nucleoproteins will be present. Under these circumstances stilbamidine evidently replaces the protein component of the cytoplasmic nucleoproteins, and thereby leads to the formation of basophilic inclusion bodies. This could also explain why no inclusion bodies in myeloma cells have been observed after stilbamidine treatment of patients in whom the change of the protein metabolism was less apparent, that is, in myeloma patients without hyperglobulinemia and without Bence Jones proteinuria.

It is perhaps unnecessary to mention that determinations of the globulins of the blood by the Howe technic (precipitation with different concentrations of sodium sulfate solutions) give only a superficial impression of the abnormalities in the globulin metabolism of the myeloma patient. The same holds true for various qualitative tests such as the formol gel test. A good example of the inadequacies of these tests is given by patient No. 1 of table 2.

The globulin content of this patient was determined repeatedly and was found to be only 2.6 per cent. The formol gel test was either negative or weakly positive on several occasions. Nevertheless, the serum of this patient must contain either an abnormal globulin or a normal globulin fraction in abnormal quantities as shown by the Sia globulin test.[9] Dilution of 0.02 c.c. of blood with 0.6 c.c. of distilled water immediately gave rise to a heavy flocculation, indicating that an abnormal globulin must have been present. This patient, as a matter of fact, developed many granules in the myeloma cells after stilbamidine treatment.

Summary

After daily intravenous injections of 150 mg. of stilbamidine basophilic precipitates developed in the myeloma cells of 12 of 13 patients who had hyperglobulinemia. Patients with multiple myeloma whose serum globulin content was normal showed much less tendency to develop these precipitates. As a matter of fact, the formation of these inclusion bodies could be observed in only five of nine myeloma patients with a normal globulin content of the serum and with Bence Jones proteinuria. In 10 patients without hyperglobulinemia and without Bence Jones proteinuria intravenous injections of stilbamidine did not result in the development of inclusion bodies.

Inclusion bodies developed after as few as seven to 10 daily intravenous injections of 150 mg. of stilbamidine had been given.

After cessation of the stilbamidine treatment the inclusion bodies persisted for many months.

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NEW DRUGS OF VALUE IN THE TREATMENT OF EPILEPSY *

By Frederic A. Gibbs, M.D., *Chicago, Illinois*

A drug that is good for one type of epileptic seizure may be bad for another; for example, Dilantin is an excellent anticonvulsant, but in many cases it increases the number and severity of petit mal seizures, and Tridione, which is often dramatically effective against petit mal, may increase the number of grand mal. Thus, in order to proceed as rationally as possible with the treatment of an epileptic patient, the type or types of epileptic seizure should be classified. The major types of epileptic seizure and the drugs which are beneficial in their treatment are shown in table 1. This table also indicates the clinical manifestations and types of electrical discharges which characterize the major types of epileptic seizure. A more detailed description of the clinical and electroencephalographic characteristics of various types of seizure is included under corresponding paragraph headings later in this article.

Classification of seizures is based on the clinical history and the electroencephalographic findings. The electroencephalogram is not absolutely essential but in most cases it makes the selection of medication easier and the results more consistent. However, even if the type or types of seizure cannot be classified, the case should be treated. The number of drugs to be tried is not great and a satisfactory result can be attained by trial and error.

The general principle of medication is as follows: Start with the drug which is presumed to be most effective. The dose should be increased to tolerance or to a level at which seizures are prevented. If the first drug reduces the number of seizures but does not prevent them the dosage should be adjusted so that no more than tolerable side effects are produced, and with this as a maintenance dose the next most promising remedy should be added. The dose of the supplementing drug should be raised to tolerance or until seizures are controlled. This procedure should be repeated with each drug in turn until seizures have been controlled or until all drugs have been tried at maximal tolerated dosage. Any drug which produces no definite benefit should, of course, be omitted, but before discarding a drug the dosage should be raised to the maximum that is tolerated. The mistake most commonly made in the treatment of epilepsy is *under-medication*, because the physician has assumed some arbitrary limit on dosage.

* Read before the General Assembly of the Illinois State Medical Society May 14, 1947. From the University of Illinois, College of Medicine, Department of Psychiatry, Chicago, Illinois.

TABLE I

Guide to Medical Treatment of Epilepsy

Type of Epilepsy	Clinical	Age	E.E.G.	Medication	Average Adult Dose†	Limiting Side Effects	Signs of Sensitivity
Grand Mal	Convulsions	Any	Slow or fast spikes and petit mal variant. (Rarely grand mal discharges)	Dilantin	1½ grs. t.i.d. after meals. Usual maximum 6 grs./day	Diplopia Staggering (May increase petit mal)	Overgrowth of gums Overgrowth of body hair Itching rash on extremities Gastric irritation
Focal	Focal convulsions	Any	Focal spikes or Focal slow waves	Phenobarbital	1½ grs. h.s. Usual maximum 3 grs./day	Sleepiness	
				Mesantoin	1½ grs. t.i.d. Usual maximum 6 grs./day	Sleepiness	Scarlatiniform rash* Fever Lymphadenopathy
				Bromides	18 grs. sodium bromide t.i.d. (Blood bromide 150–300 mg. per 100 c.c. of blood)		Acne Depression and confusion
Petit Mal (Pyknolepsy)	Frequent short lapses of consciousness. Blinking, head nodding.	Usually children	3 per second wave-and-spike	Tridione with monthly white count	4½ grs. t.i.d. or until seizures are controlled	Inability to see in a bright light Drowsiness	Hiccoughs Acneform rash Leukopenia*
				Mebaral	6 grains	Sleepiness	
Myoclonic	Lightning-like jerks	Usually children	3 per second wave-and-spike	Ketogenic diet			Loss of weight
Psychomotor	Periods of confusion with incoördination and apparently purposeful movements	Usually adults	Positive spikes. Negative spike focus in temporal lobe with spread to anterior-inferior part of head.	Any and all antiepileptic substances. (Medical treatment generally unsatisfactory.)			

* These signs of sensitivity require omission of responsible drug.

† Dose should be raised until seizures are controlled or until limiting side effects or signs of sensitivity develop.

Tonic-Clonic Convulsions

True convulsions, whether short or long in duration, whether generalized or focal in distribution, respond best to Dilantin, phenobarbital and Mesantoin.

Dilantin. Dilantin [1] has its chief use in the treatment of *grand mal* epilepsy, and any type of true convulsion. The general rule of raising the dose to tolerance, or until seizures are controlled, should be followed. Infants can usually tolerate 3 grains per day; children 4.5 grains, and adults 6 grains per day. It should be remembered that these dosages are intended merely as rough approximations.

The most usual side effects from Dilantin are dizziness, staggering and double vision. This substance is somewhat irritating to the gastric mucosa and should be taken after meals. Side effects which are encountered rather infrequently and therefore classified as sensitivities are the following: Overgrowth of the gums, overgrowth of body hair, and an itching rash, chiefly on legs and arms. All these disappear promptly on reducing the dosage or ceasing Dilantin medication.

Dilantin may increase petit mal disorder; this limits its value in certain cases. It is sometimes effective against psychomotor disorders.

Phenobarbital. Phenobarbital [2] has its chief use in the treatment of grand mal seizures and true convulsions of all types. It is usually most effective as a supplement to Dilantin. It is not ordinarily effective against petit mal. Though worth trying in cases with psychomotor seizures, in some cases it increases the frequency of the attacks. The usual and almost the only limiting side effect is excessive drowsiness, but since over-sedation is commonly misinterpreted by teachers and employers as mental retardation it cannot be dismissed as a minor complication. Unless other means of controlling seizures fail, the dose of phenobarbital should be kept below that which produces hypersomnia. The sleep-producing effect of this drug is least disturbing if it is given in a single dose an hour before bedtime. There is a wide range of tolerance, but commonly effective daily doses are: ¾ grain for infants, 1 grain for children, and 1½ grains for adults. As stated before, however, if control of seizures is not obtained on low dosage the level should be raised to tolerance.

Mesantoin. In cases of grand mal epilepsy, where Dilantin and phenobarbital are unable to prevent seizures or where the dose necessary to control seizures produced undesirable side effects, Mesantoin [3, 4] should be tried. One person in 10 is sensitive to this substance and for that reason it is ordinarily reserved until after phenobarbital and Dilantin have been tried. Sensitivity is indicated by a scarlatiniform rash, swollen lymph glands in the scalp and in the neck, and by fever. The patient should be warned to be on guard against such a reaction. If it occurs the Mesantoin should be discontinued promptly; thereafter the entire reaction will subside within two to

four days. A sensitive patient may be desensitized by giving Mesantoin in small, gradually increasing dosage, starting with approximately ½ of a grain (¼ of a tablet) per day and increasing the dose by ½ of a grain per day each week.

The usual limiting side effect encountered with Mesantoin medication is hypersomnia; therefore, it is used more advantageously in combination with Dilantin than with phenobarbital. In ordinary cases medication should be started with a dose of 1½ grains per day (¾ of a grain in young children) while the patient is maintained on whatever Dilantin and phenobarbital dosage has been found most effective and tolerable. In the second week the dose can be raised to 3 grains per day, and in the third week to 4½ grains per day. Most patients become drowsy on dosages of about 4½ grains, but the dosage should not be limited until hypersomnia develops or until seizures cease. As the Mesantoin dosage is elevated to a level producing hypersomnia the phenobarbital should be reduced.

Bromides. Bromides [5] are of limited value because their anti-convulsant action is feeble and the toxic or sedative dose is close to or identical with the anti-convulsant dose in the great majority of cases. However, if seizures cannot be controlled with other drugs recourse should be had to bromides either alone or in combination with other substances. The salt intake should be kept low and maintained as nearly constant as possible. Attempts to avoid bromide acne by the administration of iodides are irrational because such procedures are equivalent to reducing the bromide dosage; the iodides merely displace the bromides in the body.

Petit Mal Seizures and Myoclonic Jerking

The term petit mal is now used in a restricted sense to apply to a type of brief and relatively mild seizure that is most common in children. There is no tonic component. The patient stares, blinks rhythmically with an approximately three-per-second rhythm, and nods his head. Sometimes the arms are involved, or the trunk; rarely the legs. Posture is usually maintained, but consciousness is impaired or lost. The attacks usually last only a few seconds and occur many times a day. This is a general description of the petit mal seizure; any of the above features may be omitted and the patient may just stare. The finding that clinches the diagnosis is the characteristic three-per-second wave-and-spike pattern in the electroencephalogram.

Seizures of the petit mal type have been referred to as pyknoleptic seizures. When they are the only type of seizure present the case was formerly diagnosed as *pyknolepsy;* however, in view of the identity of the pathological physiology in pyknolepsy and petit mal epilepsy a separate diagnostic category does not seem necessary.

Myoclonic jerking is common in epilepsy and it is often based upon the same type of disorder as the petit mal seizure, i.e., three-per-second wave-and-spike.

Tridione. In general, the best medication for petit mal seizures and myoclonic jerking is Tridione.[6, 7] The dosage can be started at 4½ grains per day, and raised by 4½ grains each day until seizures cease, or until limiting side effects develop. However, where seizures are not occurring every day the interval between increases in dosage should be lengthened. The ordinary limiting side effects are day blindness, usually reported by the patient as photophobia or inability to see in a bright light (hemeralopia), and drowsiness. On higher dosage attacks of hiccoughing are common. These symptoms are not serious; they disappear promptly on reducing the dosage. Once seizures are controlled the patient can often be maintained on a lower dosage than that which was necessary to stop the attacks in the first place; therefore, it is in some cases desirable to raise the dosage to a high level where seizures are prevented, hold it at this level for several days in spite of toxic side effects, and gradually decrease the dosage thereafter. Many patients can be maintained seizure-free on two to four capsules per day (4½ grains in a capsule), but in some cases it is necessary to use a maintenance dose of 6 to 8 capsules per day and "shock treatment" with doses as high as 12 capsules per day may be necessary to stop the seizures. However, every effort should be made to drop the dosage, and a high level should be maintained only when it is found that seizures recur on lower dosage.

Fatal cases of leukopenia resulting from Tridione medication have been reported,[8, 9] but experience indicates that this drug can be used safely if a white-cell count and platelet estimation are obtained every month.[10] A great reduction in platelets or a white-cell count below 3000 are indications for discontinuation of Tridione therapy.

Tridione may make grand mal seizures occur more frequently. If no grand mal seizures have been reported and a subclinical grand mal component is present, the institution of Tridione medication may precipitate the first grand mal attack. In the presence of clinical grand mal, or of an electroencephalogram suggesting a grand mal component, phenobarbital or Mebaral should be used in addition to Tridione. Dilantin may be used to prevent grand mal seizures when these are found in association with petit mal, but Dilantin commonly increases petit mal disorder.

Ketogenic Diet. A diet in which sugar and starches are interdicted and in which nourishment is obtained chiefly from proteins and fats produces an altered body metabolism that is often beneficial in petit mal and myoclonic epilepsy.[11] Such a diet is expensive, difficult to maintain, sometimes distasteful and always troublesome. It is rarely effective in children over the age of ten. Such a diet may control seizures when Tridione does not and,

in cases where Tridione has given partial control, it may be used to supplement Tridione medication.

Mebaral. As a supplement to Tridione and also to reduce the possibility or likelihood of grand mal, Mebaral is of value. The dosage is double that of phenobarbital.

Psychomotor Seizures

In a psychomotor seizure the patient seems to be acting out a bad dream. Movements are more or less purposeful, though usually poorly coördinated. Such attacks have been referred to as epileptic equivalents. They are commoner in middle-aged persons than in children. Personality disorders are a frequent accompaniment.

Unfortunately, none of the substances that are useful against other types of seizures are generally effective against psychomotor attacks, and there is at present no known drug which by any stretch of the imagination can be called specific against psychomotor epilepsy. However, all remedies should be tried, and in rare cases a brilliant therapeutic result will be attained. Mesantoin should certainly be tried alone or in combination with other substances if seizures are not controlled with phenobarbital, Dilantin or Tridione. In some cases psychomotor attacks are precipitated by phenobarbital; more rarely by Dilantin.

Mixed Cases

It should not be assumed that the presence of one type of seizure excludes others. Mixed seizure and cases with more than one type are common. Petit mal attacks tend to disappear in early adult life, but sometimes they are replaced by grand mal. Grand mal attacks also tend to decrease and become less severe with increasing age, but grand mal may be replaced by psychomotor seizures. The prognosis is brightest for cases with petit mal seizures only; next, for those with grand mal, particularly the idiopathic type, and it is worst for cases with psychomotor seizures, chiefly because specific medication is lacking. Where all three types of seizure are found together the prognosis is exceedingly bad.

General Considerations Regarding Medication

Regardless of the type of seizure no case should be abandoned or allowed to continue having seizures without full trial of all anticonvulsants at maximal tolerated dosage. Since seizures and their causes are diverse a variety of remedies will probably always be necessary. The distinction between idiopathic and symptomatic epilepsy is generally valid and the drugs at present available for the treatment of epilepsy are more effective against idiopathic than against symptomatic epilepsy.

The informed practitioner will be able to treat successfully 75 per cent of patients with seizures. The remaining 25 per cent will be especially resistant cases, many with severe brain damage or additional complications. Such cases should be given access to the most advanced and expert treatment by referring them to qualified specialists. The task of the specialist will be greatly simplified if all generally available anti-convulsant substances have previously been given an adequate trial by the referring physician.

Conclusion

Since epilepsy is a common and important disorder which usually responds to medicinal treatment, physicians should be aware of the clinical and electroencephalographic features of the major types of seizure and should be able to apply with discrimination the six or seven remedies that are now of recognized value.

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INSULIN RESISTANCE *

By Arnold R. Axelrod, M.D., Sidney Lobe, M.D., James M. Orten, Ph.D., and Gordon B. Myers, M.D., F.A.C.P., *Detroit, Michigan*

It is well known that marked variations in sensitivity to insulin are found among diabetics, even in the absence of complications. This has led to attempts at classification into one of three categories, namely: (*a*) insulin sensitive, (*b*) insensitive, and (*c*) resistant. Insulin resistance is rare but is readily distinguished from the other two categories. According to the definition of Martin, Martin, Lyster and Strouse,[1] insulin resistance is present when doses of 200 units or more per day fail to reduce the blood sugar in non-acidotic patients during 48 hours' observation. This was based upon Root's calculation that depancreatized man should require 200 to 300 units of insulin daily. Although more recent observations [2, 3] have indicated that a completely depancreatized man is sensitive to insulin and requires only from 35 to 50 units daily rather than the calculated 200 to 300 units, the criteria of Martin et al. are nevertheless useful in defining the rare case of insulin resistance from the case of insulin insensitivity.

Since it has been shown that human diabetes resulting from complete pancreatectomy can be controlled on 35 to 50 units daily, insulin requirements in excess of 200 units daily cannot be ascribed exclusively to destructive lesions of the pancreas. A classification of the reported causes of insulin resistance is presented in table 1.

Table I

Classification of Causes of Insulin Resistance

A. Unavailability of administered insulin due to
   1. Failure of absorption
   2. Excessively rapid excretion
   } A possibility which has been excluded in reported cases [4, 5, 6]

B. Neutralization or destruction in blood or tissues
   1. Abnormal leukocytic activity
      (*a*) Pyogenic infection with leukocytosis [7]
      (*b*) Eosinophilia [8]
      (*c*) Leukemia [9]
   2. Excessive output of hormonal antagonists [10]
      (*a*) Anterior pituitary and/or adrenal cortex [11, 12]
         1. Cushing's syndrome [13]
         2. Acromegaly [14]
      (*b*) Hypothalamus and posterior pituitary [15, 16, 17, 18]
      (*c*) Thyroid [19, 20]
   3. Development of antibodies
      (*a*) Accompanying signs of allergy to insulin-neutralizing antibodies demonstrated [21, 22, 23, 24]
      (*b*) Allergy present but no insulin-neutralizing antibodies demonstrated [1, 5, 25, 26, 27]

* Received for publication October 24, 1946.
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(*c*) Neutralizing antibodies demonstrated but no accompanying signs of allergy [28, 29, 30, 31, 32, 33]

C. Inability of end organs to utilize insulin
1. Acidosis and/or infection [8, 30, 34, 35, 36, 37, 38]
2. Diffuse hepatic disease with defective glycogen storage and/or excessive gluconeogenesis
(*a*) Hemochromatosis [39, 40, 41]
(*b*) Acute and chronic hepatic degeneration [42, 43, 44, 45]

D. Unknown [4, 46, 47, 48, 49, 50, 51]

Thus insulin resistance has occurred under conditions which might facilitate destruction of insulin in the blood or tissues, such as in (1) states associated with abnormal leukocytic activity, e.g. leukocytosis, eosinophilia, leukemia; (2) in endocrine diseases accompanied by an excessive output of hormonal antagonists; and (3) in allergic states associated with the development of insulin neutralizing antibodies. Insulin resistance has also been reported under conditions which might interfere with ability of end organs to utilize insulin as in acidosis, infection or diffuse hepatic disease with defective glycogen storage.

Cases are encountered where no recognizable cause of insulin resistance can be found despite careful study. During the past three years we have had three such cases under observation which showed spontaneous appearance and disappearance of insulin resistance. These cases form the subject of this communication.

Case 1 (*Chart 1*). N. E., a 60 year old colored female, was first admitted on June 15, 1943. She had been in fairly good health until January, 1942 when polydipsia, polyuria, polyphagia and generalized pruritus set in. By April her weight had dropped from 160 to 130 pounds, and at that time she was hospitalized elsewhere. She was regulated on a diet with 40 units of protamine zinc insulin and 20 units of regular insulin daily, which was gradually reduced to a mere 10 units of protamine zinc insulin daily by June, 1942. Her weight at that time was 135 pounds. In July she stopped taking insulin against medical advice and in August, because of the recurrence of symptoms, she was again admitted to another hospital. The diabetes was well controlled on a diet of protein 75 grams, fat 70 grams, carbohydrates 200 grams and 40 units protamine zinc insulin daily. Her weight rose to 140 pounds. A few weeks after discharge she again discontinued her insulin injections, but she remained in good health until April, 1943 when the symptoms of diabetes mellitus were noticed again. On her own initiative she resumed taking protamine zinc insulin 40 units daily and symptoms disappeared rapidly. With the alleviation of her symptoms, she again discontinued her insulin injections; however, polydipsia, polyuria, polyphagia and pruritus recurred, leading to admission to the City of Detroit Receiving Hospital on June 15, 1943.

Past history: She had received two intramuscular injections for syphilis in 1927 and four intravenous injections in 1939. She had had three pregnancies, all of which ended in miscarriages. Her menstrual history was normal up until the age of 50 when she passed through a normal menopause. In 1923 she was told that she had a uterine fibroid. Allergic history was entirely negative. One sister, age 80, had mild diabetes. Family history was otherwise irrelevant.

Physical examination revealed an undernourished colored female, who exhibited evidence of generalized pruritus. Blood pressure 100 mg. Hg systolic and 70 diastolic, temperature 98.6, pulse 80. The pupils were equal and regular and reacted well to

accommodation but sluggishly to light. Ocular fundi revealed Grade I arteriolosclerosis. There was no diabetic retinopathy. There were early lenticular cataracts. Visual fields were normal. The pharynx, teeth and tongue were negative. There was moderate non-specific anterior cervical lymphadenopathy. A small adenoma of the left lobe of the thyroid was palpated. There were no signs of hyperthyroidism. The heart and lungs were normal. The liver and spleen were not palpable. There was no abdominal tenderness. On bimanual examination the pelvis was found to be filled with a large nodular, non-tender mass extending up to the umbilicus. The patellar and tendon Achilles reflexes were absent bilaterally. The sense of motion and position, vibratory sense and pain sense were unimpaired. The impression on admission was (1) diabetes mellitus, uncontrolled, (2) uterine fibromyoma.

Laboratory data: hemoglobin 11.5 gm.; WBC 5,750, 50 per cent neutrophiles, 42 per cent lymphocytes; 7 per cent monocytes, 1 per cent eosinophiles. Subsequent blood counts showed no significant variation. Repeated examinations of the urinary sediment were normal. Stool examinations were negative for undigested fat and meat fibers. Blood diastase was 93 units. Blood urea 20 mg. per 100 c.c. Urea clearance 95 per cent. Plasma cholesterol 364 mg. per 100 c.c. Serum calcium 9.8 mg. and phosphorus 3.6 mg. per 100 c.c. Bromsulphthalein test using 5 mg. per kg. was normal. Hippuric acid test showed 1.87 gm. benzoic acid excretion. Urinary urobilinogen was slightly abnormal on one occasion, but normal thereafter. On August 25, 1943 the serum albumin was 2.9 gm., globulin 2.0 gm. per 100 c.c.; on October 9, 1943 the serum albumin was 3.6 gm., globulin 2.8 gm. per 100 c.c. Kline test, negative. Spinal fluid, negative.

Radiological studies: Chest film revealed slight broadening of the aorta, otherwise the heart and lungs were within normal limits. A gastrointestinal roentgenographic series was negative. A roentgenogram of the sella turcica was negative. Gall-bladder visualization (Graham-Cole) revealed impaired contractility of the gall-bladder. An electrocardiogram showed myocardial damage, non-specific in type.

Repeated determinations of the basal metabolic rate gave the following results: July 23, + 17; July 27, + 18; July 30, + 13; August 11, + 41; August 16, + 33; August 21, + 35; September 10, + 22; September 16, + 28; September 20, + 18; October 5, + 26; and October 12, + 1.

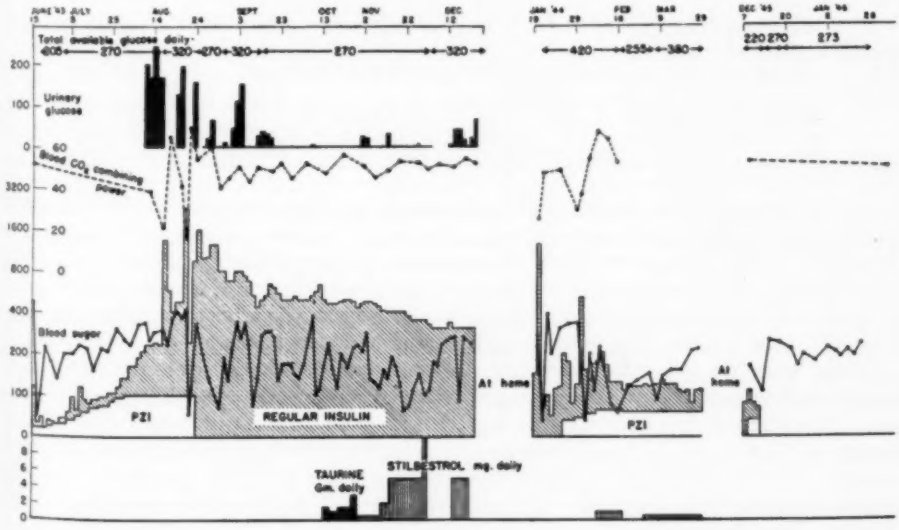

CHART 1.

The hospital course is represented graphically in chart 1. Upon admission on June 15 the blood sugar was 500 mg. per 100 c.c., and there was a 4 + glycosuria and a slight acetonuria. At seven o'clock the next morning, after a total of 20 units of protamine zinc insulin and 180 units of regular insulin given over a period of 18 hours, the blood sugar was 50 mg. per 100 c.c., the blood carbon dioxide combining power was 52 volumes per cent, and the urine was free of glucose and acetone. During the first two weeks in the hospital while on a diet of carbohydrates 150 grams, protein 80 grams, fat 90 grams with 20 to 30 units of protamine zinc insulin and 0 to 25 units of regular insulin daily, the fasting blood sugar was maintained between 100 and 230 mg. per 100 c.c. and fractional urinary specimens were negative for acetone and showed a 0 to 2 + glycosuria. The weight increased from 114 to 120 pounds during this period and the patient appeared normally sensitive to insulin.

TABLE II

Insulin Sensitivity Tests

	Date	Type of Insulin	Route	Dose Units	Blood Sugars—mg. per cent Time										
					Fasting	15′	30′	45′	60′	75′	105′	120′	180′	240′	300′
Case I (N.E.)	8–14–43	Regular	I.V.	40	266	288		380		388	354				
	8–16–43	Regular	I.V.	100	308	332		346		354					
	8–19–43	Crystalline	I.V.	150	400	398		348		344					
	10–11–43	Regular	I.V.	100	95	95	91	80	59						
	3– 9–44	Regular	I.V.	50	182	160	154	135	126						
	3–21–44	Regular	I.V.	50	172	150	146	140							
	12–11–45	Regular	I.V.	25	109	127	102	103	84				47		56
	12–21–45	Regular	I.V.	25	218		200	200	180			123	94		
	1–11–46	Placebo (Saline)	I.V.		192	169	165	154	174			157	144	140	
Case II (E.C.M.)	5–24–44	Regular	I.V.	25	332	330	338	304	308	294					
Case III (C.T.)	12–11–44	Regular	I.V.	25	240	236	240	216	220			214			
	12–21–44	Crystalline	I.V.	50	220	232	247	238	269						
	8–22–45	Regular	I.V.	25	206	204	200	202	202			194			
	8–31–45	Regular	I.V.	50	206	196	202	196	188			180			
	9– 6–45	Regular and 5 c.c. liver	I.V. I.M.	50	208	187	183	185	169			172	148		
	12–11–45	Regular	I.V.	25	216	182	183	182				183	169		
	1– 7–46	Regular	I.V.	50	140	138	146	145	130			131	131		

From June 29 until August 16 the fasting blood sugar was consistently elevated and fractional urinary specimens showed a 2 + to 4 + glycosuria, despite a progressive increase in insulin dosage to 100 units protamine zinc insulin and 140 units of regular insulin daily. Between August 9 and 15, while receiving insulin in the above doses along with a diet furnishing 270 grams available glucose daily, the patient excreted from 165 to 240 grams of glucose in the 24 hour urine specimen.

There were no local or general reactions to either form of insulin at any time. Intradermal tests with crystalline, regular and protamine zinc insulin gave no reaction. The passive transfer test was negative. There was no evidence of failure of absorption of the administered insulin. As a further check, sensitivity tests to intravenously injected insulin were performed (table 2). A thorough search for acute or chronic infection was negative. By this time it had become apparent that insulin resistance had developed.

Laboratory evidence of acidosis was first noted on August 12 when acetone appeared in the urine and the blood carbon dioxide combining power was 39 volumes per cent. Acidosis steadily deepened during the next four days. On the morning of August 16 the patient was stuporous and the carbon dioxide combining power was 21 volumes per cent. During the next 19 hours she received 2,000 c.c. Hartmann's solution, 2,000 c.c. saline and 1,500 units of regular insulin and 100 units of protamine zinc insulin. On the morning of August 17 the blood carbon dioxide combining power was 65 volumes per cent and the blood sugar was 240 mg. per 100 c.c. Despite daily doses of 400 to 610 units of insulin during the next four days, the patient slipped into severe acidosis on the morning of August 21, manifested by deep stupor, peripheral vascular collapse and a blood carbon dioxide combining power of 16 volumes per cent. During the next 16 hours she received 800 c.c. plasma, 3,000 c.c. Hartmann's solution, 1,000 c.c. saline, 2,150 units of regular insulin and 100 units of protamine zinc insulin. On the morning of August 22, 1943 the blood carbon dioxide combining power was 69 volumes per cent and the blood sugar 55 mg. per 100 c.c. Throughout that day only 250 units of insulin were required to keep the urine free of sugar and acetone. It is noteworthy that in this case, as well as in others in the literature, the hyperglycemia and acidosis in insulin resistant patients can be corrected if enough insulin is administered.

In the 16 day period from August 24, 1943 to September 10, 1943 the daily dose of insulin ranged from 700 to 1600 units of regular insulin, averaging 920 units. On a diet containing from 270 to 320 grams of available glucose, the urinary output of glucose averaged 50 grams daily. Fractional urinalyses gave 0 to 4 + glycosuria but no acetonuria. The fasting blood sugars ranged from 70 to 350 mg. per 100 c.c. Attempts at reducing the insulin dosage resulted in an increased glycosuria whereas substantial increases in the insulin dosage resulted in hypoglycemic reactions associated with blood sugars as low as 36 mg. per 100 c.c. During this period there was a definite tendency to a gradual reduction in the insulin requirement.

From September 10, 1943 to October 31, 1943, the patient was fairly well stabilized on regular insulin exclusively, the daily dosage ranging between 440 and 670 units and averaging 525 units. It was found that the diabetes was better controlled when 75 per cent to 100 per cent of the total daily dose was given in a single injection before breakfast. When a second injection was needed the optimal time was before the noon meal. A bedtime feeding was required to prevent nocturnal reactions, illustrating the prolonged effect of regular insulin when given in massive doses.

From October 15 to October 31 taurine was given in daily doses of 1 to 3 grams as a therapeutic measure, to be discussed below, but had no appreciable effect upon the diabetic state. The fasting blood sugar ranged between 100 and 250 mg. per 100 c.c. and the urine was generally sugar free.

Stilbestrol was started on October 31 in daily doses of 0.5 mg., which were increased to 2 mg. on November 10 and to 5 mg. on November 14, continuing until December 2. During this period the fasting blood sugar was generally within the normal range and the urine was usually sugar free. Insulin requirements gradually fell from 500 units at the beginning of stilbestrol therapy to 340 units at the end of the course. Stilbestrol was discontinued on December 2 in an effort to determine whether the improvement was related to or independent of stilbestrol therapy. During the following 10 days the blood sugar rose steadily and became stabilized in a zone between 240 and 280 mg. per 100 c.c. This, however, may have been due in part or in toto to a drop in insulin dosage to 320 units and an increase in dietary available glucose of 50 grams daily, rather than to estrogen withdrawal. Reinstitution of stilbestrol on December 14 in 5 mg. doses daily did not modify the hyperglycemia during the next eight days.

On December 24, 1943 the patient was discharged on a diet of carbohydrates 250 grams, protein 100 grams and fat 110 grams with instructions to take 320 units regular

insulin every morning before breakfast. No other medication was given. While at home the patient took less than the recommended doses of insulin and the diabetes was poorly controlled.

On January 19, 1944 at 11:00 p.m. the patient was readmitted, complaining of nausea and vomiting and an oppressive feeling over the precordium. She was acidotic, dehydrated, cold and pulseless. The blood pressure was unobtainable. The urine gave a 4 + reaction for both sugar and acetone. After receiving 1,275 units regular insulin and 5,000 c.c. of parenteral fluids, including 21 grams sodium bicarbonate in an 18 hour period, the patient was alert, the blood pressure was above shock level, and the urine was free from sugar and acetone. The carbon dioxide combining power of 25 volumes per cent taken nine hours after admission had risen to 42 volumes per cent nine hours later. On the morning of January 21, 1944 the blood sugar was 39 mg. per 100 c.c. and carbon dioxide combining power 45 volumes per cent.

Serial electrocardiograms were interpreted as indicative of acute ischemia of the anterior wall of the left ventricle, on the basis of deeply inverted cove-shaped T-waves associated with a normal QRS pattern in leads V_1 through V_4 inclusive. These abnormalities had completely disappeared by February 16, 1944.

During the 11 day period from January 21, 1944 to January 31, 1944 the daily insulin dose averaged only about 120 units, ranging from 50 to 200 units, and the diet contained 420 grams of available glucose. On this regimen the diabetic control was poor, the fasting blood sugars averaging over 300 mg. per 100 c.c. and the fractional qualitative urinalyses showing a 1 + to 4 + glycosuria with frequent traces of acetone. Protamine zinc insulin was started on January 26, 1944 and was given in daily doses of 40 to 65 units along with regular insulin for the remainder of the hospital stay.

On January 30, 1944 the patient had symptoms of a mild upper respiratory infection. The blood sugar was 369 mg. per 100 c.c. and the CO_2 combining power, 29 volumes per cent. She received 2,500 c.c. of intravenous fluids, including 10 grams sodium bicarbonate, on that day in addition to 175 units of insulin. On the following morning the patient was in deep stupor and the urine gave a 4 + reaction for glucose and acetone. The temperature was 103° F. and there was evidence of an early bronchopneumonia. She was put on sulfathiazole therapy and in the next 24 hours was given 1,005 units of insulin and 4,500 c.c. of fluids intravenously, including 10 grams sodium bicarbonate. Again there was a prompt response, the blood sugar and CO_2 combining power on the morning of February 1, 1944 being 28 mg. per cent and 54 volumes per cent respectively. The temperature was down to normal and remained so.

In the period from February 1, 1944 until discharge on March 29, 1944, the diabetes was fairly well controlled on a daily dose of insulin ranging from 205 to 80 units and averaging about 150 units. The dietary available glucose varied from 420 to 255 grams. On this regimen, the fasting blood sugars were usually well below 200 mg. per 100 c.c. and qualitative fractional urinalyses were consistently negative for acetone and showed a glycosuria of from 1 + to 2 +.

Stilbestrol in daily doses of 0.5 to 1.0 mg. was given in the intervals between February 7, 1944 and February 21, 1944 and from February 29, 1944 until discharge. The insulin requirement had decreased greatly before this course of stilbestrol was instituted, the diabetes being fairly well controlled with a total of 160 to 180 units of insulin and a dietary available glucose of 420 grams. Shortly before discharge the diabetes was equally well controlled with 110 to 125 units of insulin daily and a dietary available glucose of 320 grams. This slight change was probably independent of estrogenic therapy. However, the stilbestrol dosage was sufficient to cause a marked reduction in urinary gonadotropic excretion. An assay carried out by Dr. Carl Heller [52] on October 4, 1943 before the first course of stilbestrol was started gave ovarian weight of 49.2 mg. in the assay rat. The urinary gonadotropic titer was

thus in the menopausal zone but was not excessively high. Upon repetition of the assay on March 20, 1944, while the patient was receiving 0.5 mg. of stilbestrol daily, no evidence of stimulation of either the uterus or ovaries of the assay rat was obtained. This was interpreted to indicate that the gonadotropins were absent from the 12 hour overnight urine specimen or else present in quantities too small to be detected by this method of assay.

On March 24, 1944 a hippuric acid test revealed a urinary excretion of 2.65 grams of benzoic acid which showed considerable improvement over the output of 1.87 grams in August, 1943, at the time of development of the insulin resistance. The improvement was also reflected in the serum proteins. A determination on March 24, 1944 gave values of 4.4 grams per 100 c.c. serum albumin and 2.4 grams serum globulin as compared with 2.9 grams per 100 c.c. serum albumin and 2.0 grams serum globulin in August, 1943. At no time was there any clinical evidence of hepatic disease.

Insulin sensitivity tests (table 2) performed on March 9, 1944 and March 21, 1944 showed a distinct improvement as compared to those carried out during the first admission. The results of these tests together with the marked reduction in her insulin requirement indicated a change in status from insulin resistance to insulin insensitivity.

From her discharge on March 29, 1944 until her last admission on December 7, 1945, the patient was followed at frequent intervals in the Out-Patient Department. Throughout this period she took a measured diet containing approximately 300 grams carbohydrate, 100 grams protein and 150 grams fat. Weight increased gradually during 1944 and maintained a plateau during 1945. Insulin dosage did not fall below 70 units daily and averaged 100 units daily throughout the period, 60 units of which were given as protamine zinc insulin, 40 units as regular insulin. Fairly good diabetic control was maintained throughout the entire 20 months.

On December 7, 1945, the patient was readmitted to the hospital because of a head injury sustained in an automobile accident. She was conscious but suffered from a headache and vomited repeatedly during the first 12 hours. Physical examination revealed a scalp laceration, an ulcerative gingivitis, but was otherwise essentially the same as in her previous entry. The blood pressure was 155 mm. Hg systolic and 90 diastolic and pulse 74. Roentgenogram of the skull showed no evidence of fracture. Chest ray and electrocardiogram showed no significant change.

Laboratory data: hemoglobin 11.0 gm.; white blood cells 12,550, with normal differential. Blood urea was 21 mg. per 100 c.c. Prothrombin 60 per cent. Bromsulphthalein test using 5 mg. per kilo and intravenous hippuric acid test were normal. Icterus index 16.6, falling subsequently to 8.9. Serum albumin was 4.5 gm., globulin 3.1 gm. per 100 c.c. Basal metabolic rate ranged from + 14 to + 24.

The patient remained afebrile and symptom free after the first 24 hours. She was given liquids until vomiting ceased, then was placed on a diet containing carbohydrate 175 grams, protein 70 grams, fat 50 grams, which was subsequently increased to carbohydrate 200 grams, protein 100 grams, and fat 150 grams. During the first four days in the hospital the patient received 40 units of protamine zinc insulin each morning plus 30 to 40 units of regular insulin daily. The admission urine gave a 2+ reaction for glucose and was negative for acetone. The following morning, after repeated vomiting, the urine was positive for acetone and gave a 3+ reaction for glucose, whereas the blood sugar was only 153 mg. per 100 c.c. Fractional urines thereafter were negative for acetone and showed a 0 to 3+ glycosuria.

From December 11, 1945, to January 28, 1946, the patient received no insulin except on those days when the insulin sensitivity tests were run. Throughout this period the fasting blood sugars varied between 170 mg. per 100 c.c. and 260 mg. per 100 c.c., and the fractional urinary specimens were negative for acetone and showed a 0 to 4+ glycosuria. There was no evidence of acidosis at any time during this

period. She was discharged to the Out-Patient Clinic on January 28, 1946, with instructions to follow the high caloric diet and to take no insulin.

Throughout the last six months, the patient was followed at frequent intervals in the Out-Patient Department. She followed the same diet and took no insulin. Fasting blood sugars ranged between 172 mg. per 100 c.c. and 272 mg. per 100 c.c., and the fasting urine specimens showed a 1 to 4 + glycosuria with positive acetone on only one occasion. The patient has maintained her weight at 112 to 115 pounds and when last seen was without complaint.

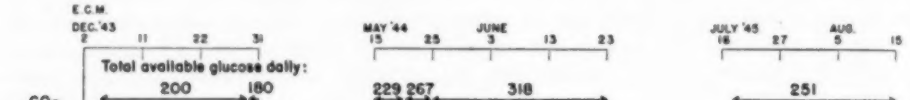

CHART 2.

Case 2 (*Chart 2*). E. C. M., a colored female, age 42, was first admitted on December 2, 1943. Diabetes mellitus had developed two years previously and had been treated at another clinic with protamine zinc insulin in doses of 120 units daily supplemented by small amounts of regular insulin. In November, 1943, the patient, on her own responsibility, gradually reduced the insulin dosage. By the end of the month she vomited repeatedly, then became drowsy and went into coma 12 hours before admission. Past history negative except for hysterectomy in 1937. There was no personal nor family history of allergy.

Physical examination revealed a well developed and nourished but markedly dehydrated female in deep coma. There was marked hyperpnea and the breath gave a strong odor of acetone. Optic fundi were negative. There was marked dental caries and pyorrhea. There were no signs of hyperfunction of the pituitary, adrenal or thyroid. The lungs and heart were negative. Blood pressure 110 mm. Hg systolic and 68 diastolic. Abdomen, back and extremities were negative. Hemoglobin 11.5 gm., white blood cells 10,200, filamentous 52 per cent, non-filamentous 22 per cent, lymphocytes 23 per cent, monocytes 2 per cent, eosinophiles 1 per cent. Blood urea was 48 mg. per 100 c.c. Blood cholesterol 139 mg. per 100 c.c.

Course during first admission: On entry the blood sugar was 520 mg. per 100 c.c., and the blood CO_2 combining power was 10 volumes per cent. The patient became mentally clear within 12 hours and acetone and diacetic acid disappeared from

the urine 20 hours after admission. During this period she received 740 units of regular insulin and 6,000 c.c. parenteral fluids. After recovery from the coma it became apparent that the patient had an upper respiratory infection which was accompanied by an average temperature of 100° F. A roentgenogram of the chest soon after admission showed congestion in both lung fields chiefly at the inner bases. All symptoms cleared within one week without complication.

Following recovery from acidosis, the patient was placed on a diet consisting of carbohydrate 150 grams, protein 70 grams, fat 100 grams and received 65 units of protamine zinc insulin daily, supplemented by 10 to 30 units of regular insulin. The fasting blood sugars ranged between 200 and 320 mg. per 100 c.c. and fractional urines revealed a 1 + to 3 + glycosuria, but were negative for acetone. Four carious teeth were extracted without complication.

On December 31, 1943 she was discharged with instructions to take a diet consisting of carbohydrate 150 grams, protein 70 grams, fat 80 grams, and protamine zinc insulin 70 units every morning plus 15 units of regular insulin before her noon meal.

On March 14, 1944 diet was increased to provide carbohydrate 200 grams, protein 100 grams, fat 120 grams which permitted slow gain in weight. As a result of gradual increase in insulin dosage to 100 units of protamine zinc insulin and 45 units of regular insulin daily, diabetes was controlled fairly well until May, 1944 when polyuria and polydipsia supervened, leading to hospitalization.

The admission blood sugar was 256 mg. per 100 c.c. and the urine gave a 4 + reaction for sugar with a trace of acetone. The patient was well hydrated, mentally clear, and in no apparent distress. Physical examination was essentially negative except for a slight decrease in vision and a slight pyorrhea.

Laboratory data: hemoglobin 12.0 grams, white blood cells 6,450. Normal differential. Blood urea, cholesterol, calcium, phosphorus were normal. Blood chlorides 518 mg. per 100 c.c. Blood CO_2 combining power 50 volumes per cent. Hippuric acid test showed excretion of 1.64 grams of benzoic acid on May 22, and 2.8 grams on June 5. Bromsulphthalein test was normal on two occasions. Serum albumin 3.6 gm. per 100 c.c., globulin 3.9 gm. per 100 c.c. Repeated urinalysis revealed normal sediment. Kline test negative. Basal metabolic rate + 1 on June 6. Chest roentgenogram revealed clearing of the previous bilateral congestion.

Clinical course of second admission: The initial diet supplied 229 grams of available glucose daily and was increased on the sixth day to provide 267 grams and on the tenth day to 318 grams. This diet was continued for the remaining four weeks of hospitalization and was distributed as follows: carbohydrate 250 grams, protein 100 grams, fat 100 grams. The initial insulin dosage of 100 units protamine zinc insulin supplemented by 30 to 50 units of regular insulin daily was inadequate and was progressively increased during the first two weeks to 150 units of protamine zinc insulin and 250 units of regular insulin daily. There was a constant glycosuria and hyperglycemia until total daily insulin dosage reached 400 units, at which time the diabetes was brought under control. The urine was consistently negative for acetone throughout this period and there was no evidence of infection. The increased insulin requirement was disproportionate to the more liberal carbohydrate intake and was attributed to increased insulin resistance. Further evidence in support of this hypothesis was obtained on May 24 when the patient exhibited no response to 25 units of regular insulin given intravenously (see table 2).

After the diabetes was brought under control the insulin requirement progressively decreased. Satisfactory control was maintained during the week prior to discharge by 50 units of protamine zinc insulin and 90 units of regular insulin daily. Crude liver extract was started at the height of insulin resistance and was given in 2 c.c. doses intramuscularly every other day for the remainder of the hospital stay. The

reduction of insulin requirements from 400 to 140 units daily which occurred during the period of liver extract administration could be explained by improved diabetic control together with spontaneous reduction of insulin resistance and thus could not be ascribed definitely to the liver therapy on the basis of the evidence at hand.

During the 13 months which elapsed since discharge from the hospital on June 23, 1944 and the patient's last admission, she was again followed at frequent intervals in the Out-Patient Department. She continued to gain weight on a diet of carbohydrate 250 grams, protein 100 grams, fat 100 grams and was maintained in fair diabetic control. The daily insulin varied from protamine zinc insulin 100 units supplemented with regular insulin 60, 60, 15, to protamine zinc insulin 75 and regular insulin 105 in mixture given in one daily morning injection.

On November 30, 1944 stilbestrol was started in doses of 1 mg. daily. On December 8, 1944 the dosage was increased to 2 mg. daily and on December 28, 1944 to 3 mg. daily. Stilbestrol was stopped on January 11, 1945, when the patient complained of swollen face and wrists. However, it was started again as 2 mg. daily January 25, 1945, and continued through February, 1945, without ill effect and without marked effect on the diabetic control.

On July 16, 1945, the patient was again admitted to the hospital in diabetic acidosis precipitated by bilateral thigh abscesses. Physical examination on admission revealed drowsiness, slight hyperpnea and moderate dehydration. Blood pressure 130 mm. Hg systolic and 90 diastolic. The remainder of the physical examination was essentially negative except for fluctuant abscesses on the anterolateral aspects of both thighs. The urine on admission gave a four plus reaction for both sugar and acetone. Blood sugar taken approximately 12 hours after admission was 298 mg. per 100 c.c. and CO_2 combining power was 20 volumes per cent. After receiving 465 units of insulin and 2,000 c.c. of parenteral fluids in a 24 hour period, the patient was alert and the urine was acetone free.

The patient's temperature ranged between 100° and 102° F. until the third day when the abscesses were incised and drained. Culture of the purulent material revealed *B. Coli* and *Staphylococcus albus*. The temperature was normal for the remainder of hospitalization. The patient was served a diet supplying 251 grams available glucose daily, distributed as follows: carbohydrate 190 grams, protein 90 grams, fat 90 grams.

Regular insulin was given at frequent intervals in accordance with urinalyses until defervescence, when protamine zinc insulin was started in dose of 35 units supplemented by 50 units of regular insulin daily. This dosage was grossly inadequate and had to be increased during the course of the next week to protamine zinc insulin 80 units and regular insulin 190 units daily in order to bring the diabetes under control.

Prior to discharge the diabetes was well controlled by daily doses of 80 units of protamine zinc insulin plus 130 units of regular insulin. Since all traces of infection and acidosis had disappeared it was evident that the patient was still insulin resistant.

The patient was discharged to the Out-Patient Department August 15, 1945, on the diet of carbohydrate 190 grams, protein 90 grams, fat 90 grams, and protamine insulin 80 units, regular insulin 130 units taken in the morning in one injection as a mixture. Soon after discharge the insensitivity to insulin gradually diminished, permitting progressive reduction in her daily insulin dosage until the total dosage dropped to 140 units (protamine 35 units, regular 105 units). The patient was without complaint, working every day and maintaining her weight.

Case 3 (*Chart 3*). C. T., a 54 year old colored male, was admitted to the hospital on October 23, 1944 because of uncontrolled diabetes and a carbuncle of the neck. Diabetes mellitus had been discovered in 1941 and was controlled on an average dose of 35 units protamine zinc insulin daily up until March, 1943, when the patient dis-

continued insulin against the advice of his physician. Shortly afterwards, polyphagia, polydipsia and polyuria set in. In November, 1943 he began to have numbness and burning of the feet. He continued at work until June, 1944, when he was forced to quit because of weakness and nervousness. Since then he had had an indolent ulcer of the right great toe. During this period he lost weight steadily in spite of a good appetite. Three days before admission a carbuncle developed on the back of the neck. During the 12 hours immediately preceding entry he vomited several times and became stuporous and delirious.

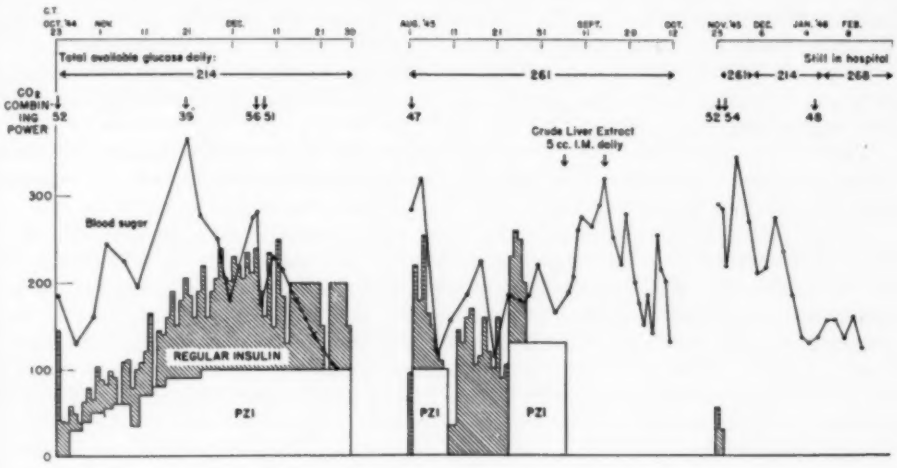

CHART 3.

Past history, including history by systems, was irrelevant. There was no personal nor family history of allergy.

Physical examination revealed a stuporous colored male, who showed no clinical signs of diabetic acidosis. The pupils were equal and regular and reacted to light and accommodation. The retinal arteries exhibited Grade 2 narrowing and sclerosis, and there were a few superficial linear hemorrhages, which were thought to be hypertensive rather than diabetic in etiology. There was no edema of the optic disk or retina. There was marked dental caries and pyorrhea. Cranial nerves were normal except for partial eighth nerve deafness on the left. The thyroid was not palpable and there were no clinical signs of hyperfunction of the pituitary, adrenal or thyroid. There was an indurated carbuncle on the back of the neck 5 by 8 cm. in diameter. The heart was moderately enlarged to the left and there was a soft blowing systolic murmur at the apex, attributed to relative mitral insufficiency. The aortic second sound was accentuated. Blood pressure 200 mm. Hg systolic and 100 diastolic. Lungs were clear. A firm liver edge was palpable one finger's-breadth below the costal margin. There was no evidence of portal obstruction. There was a small, well healed penile scar. A non-infected trophic ulcer was present on the plantar surface of the right great toe. Patellar and Achilles reflexes were absent. There was moderate tenderness over both sciatic nerves. There was hypalgesia of both feet and legs, exhibiting a jagged upper border typical of a peripheral lesion. Sense of motion and position was intact in the feet. Vibratory sense was definitely diminished over both malleoli and tibiae. There was moderate weakness of the dorsiflexors of both feet. The dorsalis pedis and left posterior tibial pulses were not obtained. The femoral and popliteal pulses were of good quality.

Laboratory data: hemoglobin 12 gm., white blood cells 10,100, 67 per cent neutrophiles, 26 per cent lymphocytes, 7 per cent monocytes. Subsequently the white blood count fell to normal. The admission urine specimen gave a four plus test for sugar, but was negative for acetone. Blood urea was 48 mg. per 100 c.c., serum albumin 3 gm. per 100 c.c., globulin 3.5 gm. Bromsulphthalein test on two occasions was entirely normal. In the oral hippuric acid test, 3.26 gm. benzoic acid were excreted. Blood Kline and Kahn tests were positive. Spinal fluid was clear and dynamics were normal. Cell count, 2 per cu. mm., 88 per cent of which were lymphocytes. The Kline test in the spinal fluid was doubtful. Colloidal gold, 2222331100. Basal metabolic rate was plus 21 on November 28, plus 40 on November 30, and plus 27 on December 5. Chest roentgenogram revealed no evidence of tuberculosis.

The clinical diagnosis was diabetes mellitus, essential vascular hypertension, peripheral arteriosclerosis, peripheral neuritis, central nervous system syphilis, possible masked hyperthyroidism.

The temperature was 102° F. on admission and rapidly fell to normal following drainage of the carbuncle. The temperature was consistently normal after October 26 and the carbuncle and the ulcer of the toe gradually healed.

Upon admission on October 24 the blood sugar was 185 mg. per 100 c.c. and the blood carbon dioxide combining power was 52 vol. per cent. The diabetes was brought under control rapidly with regular insulin and by the end of the first week it seemed well stabilized by 30 units of protamine zinc insulin supplemented by 16 units of regular insulin daily. Antiluetic therapy was instituted and continued throughout hospitalization. At this time the patient was taking a diet consisting of carbohydrate 160 grams, protein 80 grams, fat 80 grams. This diet was maintained throughout the period of hospitalization.

From November 1 until December 17, the fractional urines gave a consistent two plus to four plus reaction for glucose but were negative for acetone. Fasting blood sugars during this period ranged between 174 and 363 mg. per 100 c.c. The protamine zinc insulin was gradually increased to a maximum of 100 units on November 27 and maintained at that level until discharge. Supplements of regular insulin were given according to urinary reaction and had to be gradually increased to a range of 100 to 150 units daily when the diabetes was finally brought under control. At no time was there evidence of either local or general allergic reactions to insulin. The insulin requirements which for a time reached 250 units daily were finally stabilized at 200 units daily before discharge. There was no evidence of infection or acidosis during this period and the cause of the developing insulin resistance was not discovered.

On December 30, 1944, the patient was discharged on the same diet plus protamine zinc insulin 100 units and regular insulin 100 units, and was seen at frequent intervals in the Out-Patient Department. Throughout the first six month period, the patient persistently gained weight. His blood sugars ranged from 163 to 366 mg. per 100 c.c. with a tendency to sugars over 300 throughout the last month.

On August 1, 1945, the patient was readmitted with a history of stopping all insulin two to three weeks previously. Complaints at this time consisted of a pain behind his right ear one day in duration, staggering gait and slurring speech. Physical examination revealed a confused stuporous colored male without clinical signs of acidosis. The pupils were equal and reacted to light. Fundi revealed a Grade 2 hypertensive change in the arterioles with numerous yellowish, opaque exudate and superficial flame-shaped hemorrhages—the left fundus revealed a large fresh peripapillary hemorrhage. There was a left facial paresis and weakness in the left hand. Blood pressure 180 mm. Hg systolic and 115 diastolic. Other physical findings essentially as on first entry. On admission the blood sugar was 284 mg. per 100 c.c. and carbon dioxide combining power was 47 volumes per cent. Clinical impression: diabetes mellitus uncontrolled; general paresis.

Laboratory data: hemoglobin 10.0 grams, white blood cells 5,150 with normal differential. Repeated studies of urinary sediment were essentially normal. Blood urea 37 mg. per 100 c.c. Plasma cholesterol ranged from 414 mg. per 100 c.c. to 370 mg. per 100 c.c. Prothrombin was 82 per cent of normal. The serum albumin was 2.9 grams per 100 c.c.; globulin 4.3 grams per 100 c.c. With the intravenous hippuric acid test, 1.4 grams benzoic acid were excreted. The spinal fluid was clear and under normal pressure. Cell count 4 per cubic millimeter. Spinal fluid Kline positive. Colloidal gold, 1112211100. The chest roentgenogram revealed left ventricular enlargement. The sella turcica appeared normal on roentgen-ray.

The patient was maintained on a diet consisting of carbohydrate 200 grams, protein 90 grams, fat 90 grams throughout hospitalization. Except for the first three days after admission, the patient's course was afebrile. Only minimal residual paresis of the left hand was present at discharge.

From August 2, 1945, to August 9, 1945, patient received 100 units of protamine zinc insulin daily supplemented with regular insulin to urine reaction. Total daily regular insulin varied from 0 to 155 units. Fractional urines showed a negative to three plus glycosuria and negative acetone. Two fasting blood sugars during this period were 320 mg. per 100 c.c. and 117 mg. per 100 c.c. respectively.

From August 10 to August 23, the patient was placed on regular insulin in accordance with urinary reaction. Fractional urines varied from negative to four plus with the majority of specimens showing a three plus glycosuria, without acetonuria. The total daily insulin again varied widely, ranging from 45 to 170 units. Fasting blood sugars ranged from 114 mg. per 100 c.c. to 224 mg. per 100 c.c.

In the period from August 24 through August 27, the patient was returned to protamine zinc insulin with supplementary regular insulin. This was continued for four days and then on August 28 through September 5, 130 units of protamine zinc insulin were given daily without regular insulin. The fractional urinary specimens continued to show a negative to four plus glycosuria, no acetone. During this period, fasting blood sugars ranged between 178 mg. per 100 c.c. and 218 mg. per 100 c.c.

On September 6 until discharge, October 12, all insulin was discontinued. Between September 6 and September 15 the patient received 5 c.c. of liver extract daily intramuscularly. The fractional urinary specimens during this 10 day period showed but slight change over those of previous periods when various combinations of insulin were used. The urinary specimens varied from 0 to four plus glycosuria, but contained no acetone. Daily fasting blood sugars ranged between 189 mg. per 100 c.c. to 322 mg. per 100 c.c. with noticeable trend of rising blood sugar level toward the end of the period of liver therapy.

From September 16 until October 12, the patient received no medication. The diet was maintained at carbohydrate 200 grams, protein 90 grams, fat 90 grams. The fasting blood sugars ranged between 132 mg. per 100 c.c. (October 5) to 280 mg. per 100 c.c. Fractional urinary specimens varied from negative to four plus glycosuria and were consistently negative for acetone. The patient was discharged to the Out-Patient Department on the foregoing diet with instructions to take no insulin.

On November 25, 1945, the patient was readmitted to the hospital because of disorientation and irrationality of 24 hours' duration. Examination revealed a well developed, well nourished negro male with no clinical signs of acidosis. On first examination patient was confused, dysarthric, irrational, disoriented and generally uncoöperative. The other findings were essentially as described above. Blood pressure 190 mm. Hg systolic and 120 diastolic. On admission the blood sugar was 292 mg. per 100 c.c. and the carbon dioxide combining power was 52 volumes per cent.

Laboratory data: hemoglobin 11 grams, white blood cells 8,000 with normal differential. The admission urine specimen gave a four plus glycosuria, no acetone. The blood urea was 21 mg. per 100 c.c. Serum proteins (December 10, 1945), albumin

2.6 gm. per 100 c.c., globulin 3.9 gm.; on December 28, 1945, albumin 2.8 gm. per 100 c.c., globulin 4.0 gm. The plasma cholesterol was 231 mg. per 100 c.c. The bromsulphthalein test was normal. By intravenous hippuric acid test 0.46 gram benzoic acid was excreted. Icterus index was 10.7 on December 5, 1945, and 10 on December 28, 1945. Prothrombin 70 per cent of normal on December 4 and 100 per cent on December 28. Blood Kahn and Kline tests positive. Spinal fluid clear, normal dynamics, no cells, only trace of globulin. Spinal fluid Kline test positive. Colloidal gold 2223321100. Basal metabolic rate on December 21, 1945, was plus 7 per cent.

A low grade fever reaching a maximum of 102° (R) was present from admission to December 8, 1945, after which the temperature was normal. This fever was attributed to bronchopneumonia. The initial chest roentgen-ray revealed a small area of bronchopneumonia which gradually resolved.

From November 26 to November 30, the patient was placed on a diabetic diet consisting of carbohydrate 200 grams, protein 90 grams, fat 90 grams, and received 55 units of regular insulin the first day and 30 units the second day and none thereafter.

During the febrile period fasting blood sugars ranged between 200 and 344 mg. per 100 c.c., but urines were consistently free of acetone. After defervescence the fasting blood sugar gradually fell and finally ranged between 101 mg. and 292 mg. per 100 c.c. At this time the patient was taking a diet furnishing 268 grams available glucose and received no insulin, except on days of intravenous sensitivity tests. Even at this time a significant drop in blood sugar did not occur following an intravenous injection of 50 units of regular insulin. The mental confusion cleared within a week and throughout the remainder of the hospitalization the patient was very coöperative although his reactions were slow. A final diagnosis of paresis was made and the patient was committed to a psychiatric institution.

Experimental Studies

An experimental study was conducted to determine whether or not the alleged "insulin antagonist" [20, 21, 22, 23, 27, 28, 29, 30, 31, 32] could be detected in the sera of the three patients studied. The problem was approached in two ways, (1) an in vitro procedure in which insulin was incubated with the patient's serum for varying periods and then injected into rabbits under standardized conditions to determine its potency; and (2) an in vivo procedure in which the effect of the injection of the patient's serum on the insulin sensitivity of rabbits was determined.

Procedure

The following procedure was used for the in vitro study. A blood sample (25 to 50 c.c.) was withdrawn under aseptic conditions from the patient after 12 hours fasting and usually 12 hours after the last administration of insulin. The blood was allowed to clot, was centrifuged, and the serum was mixed with insulin of known potency. The mixture was incubated at 37.5° for varying intervals and then its potency was determined in rabbits weighing 2 plus or minus 0.5 kilos and fasted 24 hours. The Folin-Wu blood sugar method was employed. The mixture was administered intravenously in an amount containing either 5.0 units or 1.5 units

of insulin per kilo body weight. Comparable control rabbits received insulin incubated with the sera of normal subjects at the same dosage levels.

The in vivo procedure was conducted as follows: 20 c.c. of the patient's serum were injected intravenously into rabbits whose insulin response had been previously determined. After seven days, the response of the animal to a standard dose of insulin (1.5 units per kilo) was determined.

Results

The results obtained using the "in vitro" procedure are summarized in table 3.

It is evident that no indication of the presence of an "insulin antagonist" was found in any of the sera after periods of incubation with insulin, varying from 0 to 72 hours. In every case, the depression of blood sugar values in the rabbits injected with the incubated insulin-serum mixture was almost

Table III

Effect of Incubating Insulin with Patient's Sera for Varying Intervals

Time After Injection of Incubated Insulin	Blood Sugar—(mg. per cent)—Incubation Time														
	0 Hours		4 Hours		24 Hours			48 Hours		72 Hours					
						Cases									
	Control*	Case I*	Control*	Case I*	Control*	I*	II*	Control*	Case I*	Control*	Case I*	Control**	Case I**	Case II**	Case III**
Fasting	90	94	93	113	109	95	154	—	105	89	95	114	103	95	94
20 min.	58	64	52	87	60	54	41	—	76	53	62	60	60	70	48
40 min.	53	45	28	41	59	54	38	—	50	53	37	59	62	55	46
60 min.	45	45	24	35	60	45	36	—	43	49	40	64	57	63	53
90 min.	43	40	35	29	66	41	37	—	38	49	40	56	52	60	65
120 min.	39	33	23	30	58	30	37	—	43	60	43	56	45	61	82

* Dose = 5 units per kilo body weight, given intravenously to a 2.0 plus or minus 0.5 kilo rabbit fasted 24 hours.

** Dose = 1.5 units per kilo body weight.

Table IV

Effect of Injecting Patient's Serum on Insulin Sensitivity of Rabbit

Time After Insulin Injection*	Blood Sugar—mg. per cent	
	Control	Serum Case I
Fasting	114	103
20 min.	60	50
40 min.	59	52
60 min.	64	52
90 min.	56	45
120 min.	56	40

* Dose = 1.5 units per kilo body weight, given intravenously to a 2.0 plus or minus 0.5 kilo rabbit fasted 24 hours. Rabbits had been injected 20.0 c.c. of control (normal) or patient's serum 7 days previously.

identical with that observed in control rabbits given insulin incubated with normal sera.

The results obtained using the "in vivo" procedure are given in table 4.

Again there was no evidence of an "insulin antagonist" in the serum of Case 1. The response to insulin after serum administration was no different from before.

Discussion

1. Etiology of the Insulin Resistance: The known factors responsible for insulin resistance have been summarized in table 1.

In each of the three cases reported in this communication, an attempt was made to investigate each of these factors.

Failure of absorption was excluded in each case by the lack of response to intravenously injected insulin. The possibility of excessively rapid excretion was not directly investigated but was considered unlikely in view of the refractoriness to large doses of insulin given subcutaneously at frequent intervals.

No leukocytic abnormalities were found in our cases. Although no assays were made for diabetogenic hormone or adrenal steroids, the possibility of excessive output of these hormones was extremely remote in view of the lack of clinical manifestations. There was no clear cut clinical evidence of hypothalamic disease in any of our three cases but the possibility of a lesion in this region could not be excluded in Case 3 (C. T.) who was known to have central nervous system lues. In Case 1 (N. E.) and Case 3 (C. T.) the basal metabolic rate was at the upper limits of normal at the inception of the insulin resistance, and subsequently fell spontaneously to normal. Since neither patient exhibited clinical manifestations of hyperthyroidism during the period when the metabolic rate was elevated, it was felt that these readings did not represent true basal levels but merely reflected the altered metabolism consequent upon the poor diabetic control. It was also noteworthy that both of these cases had an elevated blood cholesterol instead of the depression which would have been expected if hyperthyroidism were present.

No clinical manifestation of allergy was exhibited by any of our cases. Insulin intradermal and passive transfer tests were negative in N. E. (Case 1). Incubation of the serum of each of the three patients with insulin and subsequent injection of the mixture into rabbits gave no evidence of insulin neutralizing antibodies. The fall of blood sugar of the test rabbits was almost identical with that obtained with the same animals given a similar dose of insulin which had been incubated with the serum of a normal patient. From these studies it was concluded that no insulin-neutralizing antibodies were demonstrable in the blood sera.

Each of our patients showed evidence of insulin resistance at periods when there was no acidosis and no demonstrable infection. Although none

of the patients revealed clinical signs of hepatic disease, liver function as judged by the hippuric acid tests and the level of the plasma proteins was impaired in N. E. (Case 1) and E. C. M. (Case 2) at the height of their resistance and reverted to normal after disappearance of the insulin resistance. The moderate impairment of hepatic function was probably the result of the poor diabetic control during the period of insulin resistance rather than a cause of the insulin resistance. C. T. (Case 3) exhibited gradual depression of hepatic function during the two and a half year period of observation. However, his insulin requirements were as high or higher during the first admission when his liver function tests were practically normal as in subsequent admissions when his liver function tests were impaired.

An abnormal capacity of the tissues of these patients to destroy insulin remains as a possibility which can neither be definitely established nor excluded. With this reservation these cases must be classified in the group of unknown etiology.

2. Therapy: Where the cause for insulin resistance is apparent, such as acidosis or infection, improvement may be expected upon removal of the cause. When the etiology, as in our cases, is unknown, no specific therapeutic measures are available. The necessity for giving sufficient amounts of insulin when resistance is complicated by infection or acidosis has already been emphasized. The glycosuria and acidosis under such circumstances can be controlled if adequate amounts of insulin are administered, but as much as 1,000 to 5,000 units per day may be necessary. In our cases, the diabetes was better controlled when the insulin was given in single large doses rather than in multiple smaller doses.

A diet relatively high in carbohydrates and protein was used in all three cases in an effort to increase sensitivity to insulin and to improve liver function. The amount of available glucose in the diet of each patient was varied from time to time but no direct relationship could be found between glucose intake and insulin resistance.

Taurine was administered in Case 1 (N. E.) because of the claim by Macallum et al.[53] that this substance, as well as certain other sulfone derivatives, has a marked potentiating effect on insulin in the rabbit. This observation was not confirmed in our patient.

Stilbestrol was given in Cases 1 and 2 because of claims that estrogens increase sensitivity and reduce the requirement of insulin.[54, 55, 56] Although the diabetes was somewhat better controlled (Case 1) after the institution of stilbestrol therapy on each of the two admissions, the periods on and off stilbestrol were not sufficiently long and the diabetic control not sufficiently well standardized to justify any definite conclusions regarding the effect of stilbestrol on the diabetes. The results were merely encouraging enough to justify a more adequate trial of estrogens in future cases.

The greatest reductions in insulin requirements in our cases seemed to occur spontaneously and apparently independent of therapy. For this reason, great caution must be exercised in evaluating therapeutic measures employed in patients resistant to insulin.

Summary

Three cases of diabetes mellitus have exhibited spontaneous development and subsequent recession of insulin resistance during a two to three year period of close observation.

The known causes of insulin resistance are summarized in tabular form and were investigated in each case. The investigations included studies for the presence of insulin neutralizing antibodies and were completely negative in all cases. The cause of insulin resistance in these cases remains unknown.

The necessity for giving sufficient amounts of insulin in the presence of complicating acidosis or infection has been emphasized. The maximum daily insulin requirement reached 2,150 units in one of these cases. The various therapeutic measures included taurine and stilbestrol, but it was concluded that the improvement in each case was spontaneous and unrelated to therapy.

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THE RELATIVE IMPORTANCE OF DIETARY SODIUM CHLORIDE AND WATER INTAKE IN CARDIAC EDEMA *

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The restriction of sodium chloride intake has been recognized for many years as essential in the treatment of cardiac edema. A diminished renal excretion of sodium and water is the primary factor in the production of edema according to Warren and Stead,[1] rather than increased venous pressure. Karrell's [2] once popular regimen of 800 c.c. of milk with no other food or fluid contained approximately 1.0 gm. of sodium chloride. In many hospitals at the present time, the "cardiac general" diet restricts the sodium chloride intake to a minimum of 3.0 gm. and customarily fluids are limited to 1500 c.c. daily. However, several investigators including Schroeder,[3] Schemm,[4, 5] Bridges, Wheeler, and White,[6, 7] and Leevy, Strazza, and Jaffin,[8] have recommended on the basis of clinical investigations that the sodium intake be restricted even more rigidly, and under these conditions beneficial results were obtained without restriction of water intake.

Schemm [5] attacked, as Schroeder did three years earlier, the accepted method of restricting fluids in the treatment of cardiac edema. He used a diet containing less than 2.0 gm. of sodium chloride and actually forced fluids to 5000 c.c. and over in his patients with apparently good results. Others,[6, 8] while obtaining favorable results with a free fluid intake, have not stated that they found any definite advantage accruing from forced fluids, as judged by purely clinical observation. The question as to whether water encouraged to moderate intake levels or water forced to high intake levels produces an increased loss of edema fluid (as claimed by Schemm) has not been settled. We studied this aspect of the problem.

Method of Investigation

Diet. Twenty-two patients with edema of congestive heart failure were investigated on a low salt diet of less than 1.0 gm.* of sodium chloride (14 m.eq. of sodium) and an additional eight patients were studied on the hospital cardiac general diet of 3.0 gm. (51 m.eq. of sodium). Sample one-day

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* The use of salt-free bread is essential; two analyses of ordinary bread showed 4.9 m.eq. of sodium per slice. Neo-curtesal (Winthrop Chemical Co.) has in some cases been helpful as a salt substitute after patients left the hospital. This product contains no sodium.

diets were analyzed periodically for their total sodium content, and some of these analyses included all medicines the patient received during that 24 hour period. The diet used was acid-ash, although our paramount aim was a total sodium content of under one gram.

Fluids. The fluid intake was frequently altered. Daily fluid intakes varied from 1000 c.c. to 7500 c.c. in different patients on different days. When encouraged to do so, most patients took an average of 3000 c.c. daily. Some were on fluids restricted below 1500 c.c. throughout the first week of treatment, others were forced to over 4000 c.c., while still others were restricted during the first three days of treatment and forced during the sub-

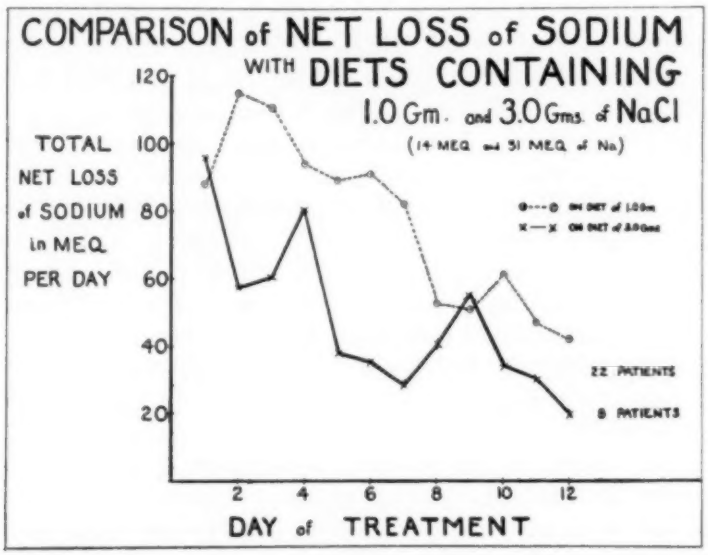

FIG. 1. Comparison of the net loss of sodium with diets containing less than 1.0 gm. and 3.0 gm. of sodium chloride (14 and 51 m.eq. of sodium respectively).

sequent four days and vice versa. These varying intakes were employed during the first seven days because, as shown below, the maximum sodium excretion occurred during the first week of the regimen. After the first week fluids were allowed as desired.

Determinations. Serum sodium and chloride levels and the carbon dioxide combining power were determined twice weekly on most patients. Twenty-four hour urines were collected daily and the total sodium ascertained by means of the flame photometer. Daily urine chloride was also determined.

Medications. All medicines known to contain appreciable amounts of sodium were avoided. No mercurial diuretics were used in any of the reported results (figures 1 and 2) either during or for at least two weeks before treatment was begun so that the effect of diet and fluids on sodium excretion could better be evaluated. Some of the cases did receive am-

monium chloride or ammonium sulfate. All patients were fully digitalized at least 36 hours before the regimen was started except for four who did not receive digitalis until the edema had subsided. All had congestive heart failure with clinical evidences of edema.

Results

Sodium Intake and Excretion. Daily determinations of the 24 hour urinary output of sodium were averaged irrespective of fluid intake for each of the two dietary regimens. The net loss of sodium was calculated by subtracting the dietary intake from the 24 hour urinary excretion and adding

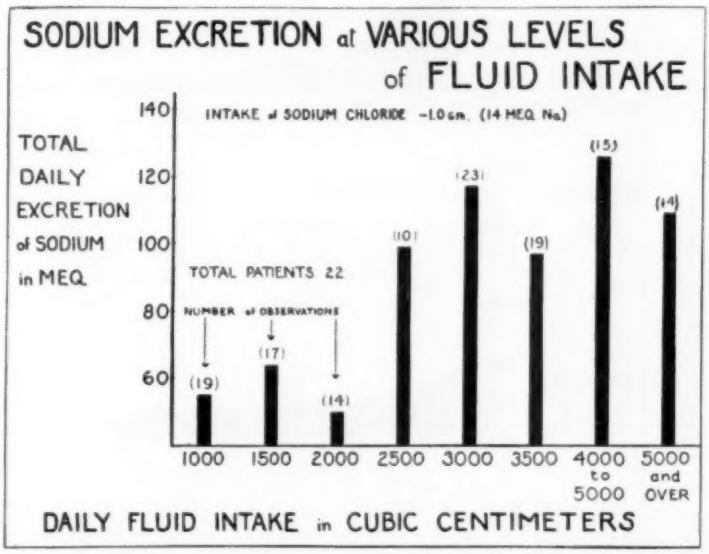

Fig. 2. Total daily sodium excretion at various levels of fluid intake.

20 m.eq. allowed for skin and fecal loss (see below). In general, chloride excretion paralleled that of sodium, but the chloride intake was not determined. A comparison of the two diets (figure 1) shows that the net loss of sodium on the diet of less than 1.0 gm. of sodium chloride is appreciably greater than on the diet of 3.0 gm. The maximum sodium loss is achieved during the first seven days of treatment, and after this period a moiety is excreted at a relatively constant rate. Particularly on the 1.0 gm. diet (actually 14 m.eq. of sodium), the excretion rate of sodium seems more closely related to its load in the body at the time when the low salt intake regimen is begun. Fluid intakes varied at random for any particular day of treatment so that the decreasing sodium loss can not be attributed to a decreasing fluid intake.

Total Fluid Intake and Sodium Excretion. Average 24 hour sodium excretions at various levels of fluid intake were calculated for those cases on

the diet containing less than 1.0 gm. of sodium (figure 2). Only values obtained during the first seven days are included. The total sodium excretion on a daily fluid intake of 1500 and 2000 c.c. was only about half that which occurred when the fluid intake was 3000 c.c. The difference was shown to be statistically significant.

Clinical Results. Very satisfactory clinical improvement was noted in the majority of our 22 patients treated with the less than 1.0 gm. sodium chloride diet. Seven cases showed an excellent response with rapid clearing of large amounts of edema, as illustrated by Case 1 (figure 3). Ten cases

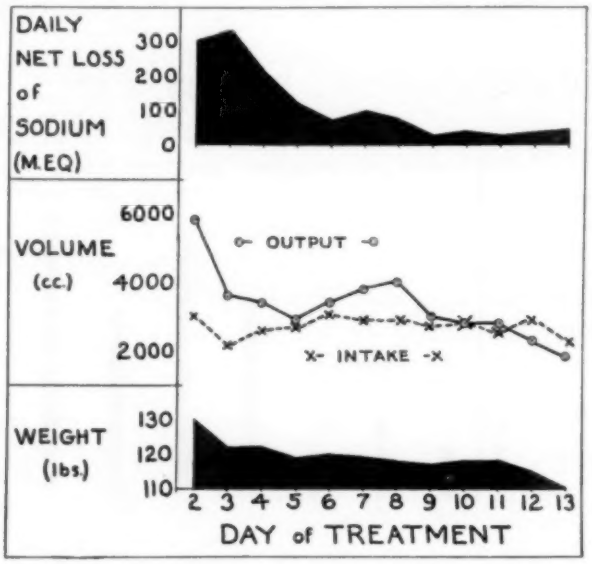

FIG. 3. (*Case 1*) Rapid loss of edema with the less than 1.0 gm. sodium chloride diet and moderate fluid intake.

showed slower but satisfactory clearing of edema. In five cases maintained four to 15 days on the less than 1.0 gm. sodium chloride diet there was no apparent clinical improvement (Case 2, figure 4).

The majority promptly lost an average of 1½ lbs. per day. Some showed a urinary output actually exceeding the water intake. Most cases had a negative water balance even when the urine output was less than the water intake, reflecting extrarenal water loss of approximately 1000 c.c. per day. These effects were achieved without recourse to mercurial diuretics. Clinical evidences of edema disappeared usually within one week.

No adverse effects were noted which could be directly attributed to the ingestion of extra water. However, five of the patients with chronic edema of long standing responded very poorly to the diet and ingestion of water alone. In these cases it was felt that the use of mercurial diuretics was mandatory. None of these patients seemed to show increased edema before administration of mercurial diuretics. Three of these patients slowly im-

proved. One with hypertensive heart disease died in uremia after 17 days' treatment. Another with arteriosclerotic heart disease and congestive failure died of far advanced active pulmonary tuberculosis.

Illustrative Case Reports

Case 1. (Figure 3) E. E., a 62 year old white male, admitted for the fourth time during the past six years with congestive failure due to hypertensive arteriosclerotic heart disease. He had discontinued digitalis therapy one month before admission. Physical findings included the liver edge palpable 8 cm. below the right costal margin. There were 3 + pitting edema of both lower legs and small pleural

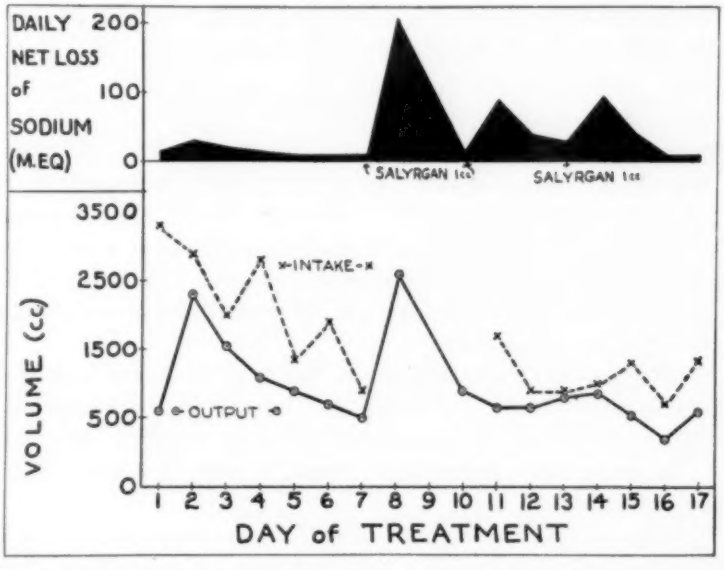

Fig. 4. (*Case 2*) No clinical improvement with the less than 1.0 gm. sodium chloride diet and a low fluid intake.

effusions bilaterally. Digitalization was carried out on admission and two days later the regimen was begun. On the less than 1.0 gm. sodium chloride diet and a moderate fluid intake he improved rapidly and was free of visible edema within one week. The response of urinary output greater than the corresponding fluid intake was unusual and occurred in only seven of our patients.

Case 2. (Figure 4) D. D., a 36 year old white woman, admitted for the fourth time during the past three years with congestive heart failure. She had had rheumatic heart disease since age eleven. No digitalis had been taken recently. Physical findings included the liver margin 6 cm. below the right costal margin, mild ascites, and 3 + pitting edema of both lower legs and sacrum. Blood pressure was 210 mm. Hg systolic and 100 diastolic. Phenolsulfonphthalein excretion test 65 per cent after two hours. She was promptly digitalized on admission and the regimen begun two days later.

Comment. This patient was so weak that she could not be weighed and no clinical improvement was manifest after one week of treatment. Mercurial diuretics were subsequently employed but even then her response was

very slow and she still had some edema two weeks after admission. Improvement finally warranted discharge after 32 days of hospitalization.

Despite such low sodium excretions as the occasional values of 2 m.eq. for a 24 hour period, this patient probably had a negative sodium balance resulting from extrarenal losses of the order of 20 m.eq.[9, 10, 11] and a dietary intake of 14 m.eq. of sodium per day. The daily fluid intakes were low, but the patient's distressing symptoms of congestive failure precluded the ingestion of more water. At the estimated rate of a daily net loss of 8 m.eq. of sodium (only 2 m.eq. in the urine) many days would have elapsed before any appreciable loss of sodium had occurred. Under these circumstances even increasing the fluid intake to double the urine volume would only have increased the sodium excretion by about 2 m.eq. more per day.

Discussion

In general the clinical responses of our patients seemed to depend on their ability to excrete sodium. Where the sodium chloride excretion was very low, the patients responded poorly. Although forcing fluids caused some increase in sodium and water loss, the slightly negative sodium balance was seemingly not enough to affect the clinical course. However, in none was there any adverse effect from the ingestion of copious amounts of water when the diet was kept low in sodium.

In some patients the concentration of sodium in the urine was higher than in those mentioned above.* An increase of urinary volume following an increased water intake resulted in a corresponding increase of total sodium excretion. In these cases large water intakes were of much value in augmenting the sodium loss.

This regimen is not considered a substitute for mercurial diuretics, especially in the more refractory cases. The relative sodium loss of three to five days on the regimen for the average patient was only the equivalent of that obtained by 1 c.c. of Salyrgan. Nevertheless, the low sodium diet and moderate intake of water (3000 c.c. daily) appear to be most valuable adjuncts to digitalis and the mercurials in the treatment of cardiac failure.

The Theory of the Regimen. Cardiac edema is associated with certain aberrations in renal function. This disturbance in renal function is manifested preëminently by the inability of the kidney to eliminate sodium and chloride in the same manner as the normal kidney. This is correlated with the lack of concentrating power for these ions, as noted by Futcher and Schroeder [12] for chloride and by us for sodium. There is no evidence that the ability to dilute these ions in the urine well below plasma levels is significantly different from normal. This relatively normal diluting ability of the kidney in cardiac edema may be used to evaluate the importance of low salt and high water intake in relieving cardiac edema.

* Before the regimen was begun the urinary sodium concentration was rarely as high or higher than the serum concentration. This observation parallels that of Futcher and Schroeder [12] on chlorides.

A quantitative theoretical basis for the dehydrating action of water in normal man has been discussed by Wolf.[13, 14, 15] It was shown that when a salt : water intake (as a solution) is steadily maintained below about 15 to 20 m.eq./l there is a renal leakage of salt in excess of intake. This critical concentration was called the minimal isorrheic concentration or MIC. But the normal plasma levels of sodium and chloride are protected. More water is excreted than is taken in and this steady dehydration prevents a fall in electrolyte concentration which would otherwise occur as a salt deficit developed. It is considered a tenable hypothesis that this mechanism operates in the cardiac patient.

The experience of others as well as our own has established that with diets containing 3 to 4 grams of salt no appreciable loss of edema follows the administration of moderate or fairly high water intakes. We may consider a case of a daily salt intake of 68 m.eq. (4 grams) and a water intake of 3 liters. The extrarenal salt loss is taken as 20 m.eq. per day.* Thus the ratio of *dietary salt* increment to the *dietary water* increment offered to the kidney is

$$\frac{\text{salt}}{\text{water}} = \frac{68 - 20}{3} = \frac{48}{3} = 16 \text{ m.eq./l.} \qquad (1)$$

This ratio, which would characterize the total daily salt and water intake if they were taken as a solution, may be called the "effective intake concentration" of salt (sodium).

Since cardiacs ordinarily maintain essentially normal or constant plasma concentrations of sodium and chloride and since they seem to be in water balance at the edema level when the effective intake concentration is approximately equal to the normal MIC as above, it would appear that a MIC in the cardiac can be of the same magnitude as that of the normal.

On a 2 gram diet (34 m.eq.) with the same water intake as above, we would have

$$\frac{\text{salt}}{\text{water}} = \frac{34 - 20}{3} = \frac{14}{3} = 4.7 \text{ m.eq./l.} \qquad (2)$$

This effective intake concentration, being considerably lower than the MIC, is conducive to the removal of edema. If the cardiac behaves as the normal with regard to this principle of dehydration (figure 1 shows how the leakage of sodium increases as the effective intake concentration is lowered), then still lower salt intakes providing lower effective intake concentrations of salt should remove edema more readily.†

* The quantity of preformed and oxidative water of the food is approximately offset by the extrarenal water loss; they are omitted for simplicity.

† In practice our salt intakes of 14 m.eq. per day provided effective intake concentrations of salt of zero, or even negative values. The results attest to the advantage of such low values.

If the 4 gram diet above were to be complemented with sufficient water to give an effective intake concentration of 4.7 m.eq./l as in the 2 gram diet of equation (2) then

$$\frac{\text{salt}}{\text{water}} = \frac{68 - 20}{10.2} = \frac{48}{10.2} = 4.7 \text{ m.eq./l.} \quad (3)$$

That is, over 10 liters per day would theoretically be required to offset the extra salt.* Practically this fluid intake is almost impossible to attain and experience shows it is undesirable. These computations indicate that low salt intake is relatively more effective than high water intake in this treatment of edema; and that the key to successful treatment is not the low salt or the high water per se. Rather the basic mechanism of the therapy is a low effective intake ratio of salt to water. This is more easily obtained in practice by lowering salt intake than by raising water intake. The degree to which the latter can be carried out falls short of theoretical requirements when salt intake is not sufficiently restricted.

Summary and Conclusions

On a diet containing less than 1 gm. of sodium chloride daily 22 patients with edema of congestive heart failure were investigated and an additional eight patients were studied on the hospital cardiac general diet containing 3.0 gm. of sodium chloride. Total daily urinary sodium and chloride excretions were observed with varying fluid intakes.

1. From these studies it was believed that the net loss of sodium and of edema in patients with cardiac failure is greater when a diet containing less than 1.0 gm. rather than 3.0 gm. of sodium chloride is used.

2. The net loss of sodium and of edema is also greater when patients are encouraged to take 3000 c.c. of fluid daily rather than be restricted to the customary 1500 c.c. There seems to be little added benefit from attempting to force fluids above 3000 c.c.

3. It is suggested theoretically that the fundamental object of the regimen described to treat cardiac edema is the maintenance of a low ratio of sodium intake to water intake rather than a low sodium or a high water intake per se. This concept provides a basis for evaluation of the relative importance of dietary salt and water in this regimen; and it accounts quantitatively for the fact that restriction of salt to low intakes is more readily effective in relieving cardiac edema than forcing fluid to very high levels.

* The same effective salt: water intake concentration at two different rates of water intake does not imply the same rate of dehydration. The theoretically higher rate of dehydration at higher water intakes varies with the salt intake.[14] It is often insignificant as said earlier. For each extra gram of salt added to the diet it may be estimated that from one to several liters of extra water would have to be added to maintain the same rate of dehydration in the edema patient. But this computation cannot be made at all accurately because of the changing character of salt excretion as the patient proceeds to reduce his edema salt load.

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THE PROGNOSIS OF SYPHILITIC AORTIC INSUFFICIENCY *

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THE course of syphilitic aortic insufficiency is generally believed to be rapidly progressive.[1, 2, 3, 4, 5, 6] Death from cardiac failure is said to occur 12 to 36 months after the discovery of the lesion,[7] although Grant [8] in a study of 1,000 cardiac patients showed that the 10-year case fatality rate of syphilis of the aortic valve is only 64 per cent. It has been reported that antisyphilitic therapy doubles the life expectancy in this disease.[3]

In a previous study from this clinic [9] of a large group of patients with aortic valvular syphilis, it was observed that current prognostic data based on the course of the disease following the onset of symptoms of failure were inapplicable, as the disease is characterized by an asymptomatic phase of two to 10 years' duration. The present study represents a continued investigation and follow-up of these same patients.

In the earlier study, a group of 91 patients with syphilitic aortic insufficiency was followed, and the period of observation, presenting complaint, and ability of these patients to work were determined. They were classified into three groups according to whether they were asymptomatic (I), had symptoms on questioning only (II), or were symptomatic (III). Patients in Group I denied any exertional or paroxysmal dyspnea, cough, palpitations, substernal or precordial pain, orthopnea, or ankle edema. Those in Group III presented one or more of these symptoms, most commonly exertional dyspnea. The Group II patients had not sought medical attention for these symptoms, but acknowledged one or more of them after specific questioning. Forty-seven of these 91 patients were available for determinations of circulation time, venous pressure, vital capacity, cardiothoracic ratio, and blood pressure. It was found that, in the group studied, aortic insufficiency due to syphilis was present in a clinically recognizable form for two to 10 years before the development of symptoms. The asymptomatic phase was encountered in approximately one-half of the patients with valvular syphilis.

Materials and Methods. In the present investigation, 27 of the 47 patients previously studied were available for a repetition of the observations carried out five and one-half years previously. Three additional patients were known to be alive, but could not be located at the time clinical deter-

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minations were repeated. Thirteen had died, and reliable information as to the circumstances of their deaths was obtained. Autopsies were performed in three of the 13 cases, and the diagnosis of syphilitic aortic insufficiency was confirmed in all three. Determinations of circulation time,[10] venous pressure, vital capacity, blood pressure, and heart width were repeated on each of the 27 patients available for these studies in the same manner as they had been performed previously, with two variations. Calcium gluconate was used for arm-to-tongue time in a few patients because decholin was not available. There is no significant difference in the circulation time as tested by these two materials.[11] Estimated heart width calculated by means of Ungeleider's tables [12] was substituted for the cardiothoracic ratio. These findings are presented in table 3.

The diagnosis of syphilitic aortic insufficiency was made by demonstrating the presence of a diastolic murmur over the aortic area, and/or down the left sternal border, in a patient known to have had syphilis and who had no evidence of mitral stenosis or congenital heart disease either clinically or by roentgen-ray. The murmur was confirmed by at least two different observers, and patients were separated into two groups according to the quality of the diastolic murmur. When the murmur was easily audible in the recumbent position, it was called "loud." When it could be heard only by having the patient sit up, lean forward, and hold his breath in expiration, it was called "soft."

Roentgenograms of the chest were obtained on each of the 27 patients to determine heart size and aortic width as compared with heart size and aortic width noted in the earlier study. The width of the ascending aorta was determined by measuring the ascending aortic shadow on a left anterior oblique or left lateral chest roentgen-ray film. Four centimeters was accepted as the upper limit of normal width. The width of the heart was measured as the greatest transverse cardiac diameter on a two-meter roentgen-ray plate.

Classification of patients into the three groups according to symptoms was retained, and the individual patients were reassigned accordingly to their present symptomatology, as in table 5. Patients were also tabulated (table 4) according to their ability to work at the time of the original survey and again at the time of the present study, five and one-half years later. Period of observation, duration of asymptomatic phase, duration of life after onset of symptoms, age, sex, and color are recorded in table 1.

Observations. Forty-three patients were followed for two to 16 years. At the time of the present study, 30 of these were alive. The group as a whole were doing remarkably well, even though the presence of aortic insufficiency had been recognized six to 12 years previously. The asymptomatic phase of the disease in this group lasted two to 10 years, and the duration of the symptomatic phase of the disease was even longer, two to 14 years. In the five and one-half years of the investigation, the status of 20

TABLE I

Name	Age	Race	Sex	Years of Observation	Asymptomatic Phase, Years	Symptomatic Phase, Years	Years Alive after Diagnosis	Age at Death
Group I								
BJ	43	W	F	5	5		5	
JF	68	B	F	7	6	1	6	
SM	60	W	F	8	2	5	7	
EG	59	W	F	10	6		6	
HJ	63	B	F	6	6	1	6	
JM	50	W	M	10	10		10	
BA	59	W	F	10	10		10	
MZ	69	W	M	11	5	2	7	
DF	63	W	F	7	7		7	
SK	60	W	M	7	6		6	
JE	77	B	M	9	7	2	9	
MMc	77	W	F	11	6	5	11	
MG	64	W	M	9	7		7	
MF	45	W	F	7	7		7	
MD	47	W	M	6	6		6	
MV	62	W	M	10	10		10	
CK	51	W	M	4	4		4	
BF		W	F	6	0	3	3	46
AW		W	M	8	8		8	63
HM		W	M	8	8		8	81
Group II								
GF	54	W	F	7	7		7	
FW	75	W	F	9	?	9	9	
LL	77	W	M	16	0	6	6	
FK	61	W	M	8	3	5	8	
HJ		W	M	5	5		5	64
JB		W	M	3	?	3	3	60
JMc		W	M	4	?	4	4	73
Group III								
RK	48	W	F	7	0	6	6	
JG	53	W	M	11	?	11	11	
AC	57	W	F	9	0	7	7	
AM	60	W	F	8	2	7	8	
MB	71	W	M	8	0	7	7	
JH	35	B	F	8	?	8	8	
GW	50	W	F	7	?	7	7	
WW	49	W	M	8	?	14	8	
SW	60	W	M	12	?	12	12	
CB		W	M	5	?	5	5	71
GL		W	M	2	?	2	2	60
JK		W	M	3	2	2	3	77
JMc		W	M	4	?	4	4	67
JP		W	M	5	?	5	5	42
FN		W	M	2	?	7	2	69
NM		W	M	2	?	3	2	55
	Range:			2–16	2–10	2–14	2–12	42–81
	Average:			7.2 yrs.	6.0 yrs.	5.6 yrs.	6.5 yrs.	63.4 yrs.

of the 43 patients had changed. Only six of the group previously reported as asymptomatic have developed symptoms in the interval. Thirteen of the whole group have died, and seven had to be reclassified as symptomatic-on-questioning or frankly symptomatic.

TABLE II

Group	Follow-up in Years	No. of Patients	Living	Died of Heart Disease	Died of Other Cause
I (Asymptomatic)	6–12	21	18	1	2
II (Symptoms on Question Only)	5–16	6	3	1	2
III (Symptomatic)	2–12	16	9	6	1
Total	2–16	43	30	8	5

In table 3 may be seen a comparison of the data concerning cardiac efficiency obtained in the present study and the values noted five and one-half years previously. A significant elevation in the circulation time above normal was noted in 12 patients, and the highest value was 26 seconds. In the present study, the venous pressure determinations were elevated in 14 patients, whereas previously all but one were within normal limits. The vital capacities were below 70 per cent of normal in 13 patients. Previously, eight were below 70 per cent. Twelve patients had widening of the ascending aortic shadow, two having developed this in the previous five and one-half years. Eight of the patients presented a combination of two or more of these positive findings, thus showing a correlation among the various indices.

A striking feature of almost all these patients was their ability to continue their usual pursuits; and, with one exception, all were well-compensated despite their age and the duration of their known aortic insufficiency (6 to 12 years). Indeed, one who was unable to work at the time of the previous evaluation has become asymptomatic and able to work as a switchboard operator 30 hours a week. This has been tabulated in table 4.

Of the 27 living patients, 12 have remained completely asymptomatic. These work as: a janitor for a 48-family apartment building, a full-time waiter, a chauffeur, a machine operator, a furrier, a cook and a housewife. Two patients who were originally classified as asymptomatic have been placed in Group II; one is confined to a mental institution, and the other is a janitor for an apartment house. Four of the patients in the original Group I are now in Group III, but they are doing approximately the same amount of work as they did five and one-half years previously. All these latter patients are in the seventh and eighth decades of life. The one patient in Group II who has been placed in Group III is 75 years old and unable to work. In 1941 she did housework. Thirteen of the original group of 43 patients have died, eight of them because of heart failure. The average age

TABLE III

Determinations of Cardiac Efficiency

(Upper figure, 1941 study; lower figure, 1946)

Name	Circulation Time	Venous Pressure	Vital Capacity	Per Cent Normal	Blood Pressure	Pulse Rate	Aortic Widening	Heart Width	Estimated Heart Width	Quality of Diastolic Murmur
					Group I					
BJ	10.2	79	2350	78	150/85	116	0	112	118	soft
	11.8	197	2300	78	160/80	90	0	110	121	
JF	10.7	60	2000	74	160/80	100	0	102	106	soft
	13.0	150	1900	70	200/90	88	0	108	107	
SM	11.4		2700	74	140/80	72	0	120	121	soft
	19.5	175	2200	70	130/80	80	0	120	128	
EG	12.0	100	2300	80	150/70	64	0	124	124	soft
	15.0	105	2100	70	140/78	62	0	125	125	
HJ	12.1	50	2000	74	170/90	88	+	130	121	loud
	13.5	107	1800	68	190/80	66	+	131	119	
JM	12.5	70	3800	90	180/90	84				loud
	19.0	180	3200	69	240/110	84	+	150	132	
BA	14.0	90	2800	80	190/54	80	+	155	140	loud
	16.5	215	2300	66	250/80	72	+	183	145	
MZ	15.8	115	2500	60	190/80	76				loud
	23.0	120	2000	48	220/88	68	+	170	129	
DF	16.9	44	1900	54	190/90	112	0	150	139	loud
	14.5	100	1800	50	220/80	92	0	160	145	
SK	17.3	88	3400	89	140/70	66		145	119	soft
	18.5	95	3400	89	156/70	60	+	130	115	
JE	18.1	51	3350	80	170/90	74	0	110	113	soft
	23.0	81	3200	77	172/88	74	0	115	113	
MMc	18.4	88	1400	38	162/82	90	+	150	153	soft
	25.0	105			150/75	82				
MG	18.5	70	2200	55	180/90	68	0	139	118	soft
	22.0	60	2000	50	178/88	72	0	140	120	
MF	11.0	70	2400	70	150/82	84	0	130	132	soft
	15.0	155	2900		160/90	88	0	130	140	
MV	17.0	68	2900	62	125/60			140	132	soft
	17.0	170	3000	67	150/70	72		145	134	
MD	14.5	94	3500	80	130/60	100		115	120	loud
	14.0	130			150/50	98				

TABLE III—*Continued*

Name	Circulation Time	Venous Pressure	Vital Capacity	Per Cent Normal	Blood Pressure	Pulse Rate	Aortic Widening	Heart Width	Estimated Heart Width	Quality of Diastolic Murmur
Group II										
GF	12.7		2000	70	188/86	96	0	104	118	soft
	17.0	110	1800	61	160/60	90	0	105	115	
FW	14.4	78	1600	45	214/78	72	+	150	148	loud
	25.0	130	1600	45	220/70	76	+	135	123	
LL	15.6	50	2700	78	208/80		0	133	130	loud
	24.0	98	2100	50	230/80	72	+	158	130	
Group III										
RK	14.1	102	2700	90	180/90	116	0	105	112	none?
	17.5	175	2300	74	210/100	84	0	110	116	
JG	14.7	85	2800	63	160/60	88	0	160	122	loud
	26.0	85	2200	51	140/40	96	+	167	123	
AC	14.9	82	2300	81	180/60	80	+	132	122	loud
	27.0	172	2200	71	230/50	70	+	150	122	
AM	16.3	99	1750	58	212/110	96	0	135	142	soft
	18.0	192	1400	50	228/100	90	0	138	136	
MB	16.6	97	2600	53	145/60	88	+	170	142	soft
	23.0	200	2200	44	172/60	88	+	184	146	
JH	17.9	130	2000	76	158/32	84	+	148	111	loud
	17.0	172	2000	76	186/40	82	+	155	107	
GW	22.5	50	2000	70	170/45	100	0	133	112	loud
	17.5	70	2000	70	138/42	72	0	117	112	
WW	15.0	90	2200	46	140/50	92		147	133	loud
	23.5	190			156/74	90	+	148	133	
Group IV (dead)										
BF	13.9	95	2000	66	270/145	92	+	135	127	soft
AW	15.0	92	3150	85	168/64	72	+	146	136	loud
HM	16.6	80	2400	56	210/70	88				soft
HJ	13.6	37	2500	75	135/60	118	0	120	121	soft
JB	22.4	65	3100	76	170/65	80	0	160	136	loud
JMc	29.8	135	1850	42	200/65	72	+	175	134	soft
CB	14.5	98	2000	45	190/70	80	0	140	125	soft
GL	19.7	86	2700	72	150/40	80	+	154	110	loud
JK	22.8	117	2500	56	165/50	80				loud
JMc	23.8	82	2400	59	220/90	52	+	190	125	loud
JP	24.6	72	2500	64	194/50	80	0	173	133	loud
FN	28.2	52	2000	41	140/70	64	+	168	138	soft
NM	28.8	53	3000	65	170/15	112	+	182	128	loud

at death was 63.4 years, an average of 4.4 years (one to seven years) after the diagnosis of aortic insufficiency was made.

Examination of table 6 shows that among all the living patients, aortic insufficiency has been recognized for an average of 7.6 years (5 to 12 years). There is no marked difference among the three groups as to the time their aortic insufficiency was discovered.

TABLE IV

(Upper figure 1941; lower, 1946)

Name	Age	Type of Work	Hours per Day
		Group I	
BJ		Nursemaid for two small children	Full-time
	43	Machine operator, biscuit factory	8
JF		Apt. house supt. and housework for 2	9
	68	Apt. house supt. and housework for 2	
SM		Sewing (also helps with housework)	6
	60	Sewing (also helps with housework)	
EG		Housework for two	
	59	Furrier	7
HJ		Nursemaid (four children)	Full-time
	63	Housework for self (3½ rooms)	
JM		Chauffeur	Full-time
	50	Chauffeur	
BA		Cigar maker (2 days a week, own housework)	10
	59	Own housework	
MZ		Salesman	5–6
	69	Unemployed—able to work	
DF		Housework for self and four others	
	63	Housework for self and four others	
SK		Janitor for 44-family building	15
	60	Janitor for 48-family building	16
JE		Unemployed—able to work	
	77	Unemployed—able to work	
MMc		Housework	
	77	Confined to mental hospital, ambulatory	
MG		Waiter	8
	64	Waiter	8
MF		Cook	6–8
	47	Cook	8
MD		Taxi driver	8
	46	Truck driver	8
MV		Carpenter	8
	62	Cabinet maker	12

TABLE IV—*Continued*

Name	Age	Type of Work	Hours per Day
		Group II	
FW	75	Housewife—housework for two Unable to work	
LL	77	Waiter Waiter	6 5
		Group III	
RK	48	Housework for three Housework for three	
JG	53	Unemployed—able to work Boatswain	7
AC	57	Housewife—housework for two Housewife—housework for two	
AM	60	Housewife—housework for two Housewife—housework for two	
MB	71	Bartender Bartender	9/week 8
JH	35	Housewife—housework for two Housewife—housework for two	
GW	50	Unable to work Switchboard operator	4
WW	49	Salesman Salesman	4 8
		Group IV (dead)	
BF	46	Head matron, department store	8
AW	63	Unemployed—able to work	
HM	81	Salesman	?
HJ	64	Decorator	7
JB	60	Unemployed—paresis	
JMc	73	Unemployed—osteomyelitis	
CB	71	Housework—one room	
GL	60	Actor—unable to work	
JK	73		6–8
JMc	67	Unable to work	
JP	42		2–3
FN	69	Unable to work	
NM	55	Unable to work	

Table 7 illustrates the age distribution of those who died directly because of their heart disease.

Nine of the symptomatic patients, groups II and III, have been maintained on digitalis with improvement in compensation for two to six years. Of the 13 who died, nine were digitalized, all for at least two years, and one

TABLE V

Changes in Classification of Patients

Group	February 1941	January 1947			
		Group I	Group II	Group III	Dead
I	21	12	2	4	3
II	6	—	2	1	3
III	16	—	—	9	7
Total	43	12	4	14	13

TABLE VI

Patients Living, January 1947

Group	No. of Patients	White		Colored		Ages	Average Age	Average Years Aortic Insufficiency Known
		Male	Female	Male	Female			
I	17	7	7	1	2	43–77	62.5	7.3 (5–11)
II	4	2	2	0	0	54–77	68.7	7.5 (6–9)
III	9	4	4	0	1	35–71	53.4	8.2 (6–12)
Total	30	13	15	1	3	35–77	58.9	7.6 (5–12)

TABLE VII

Patients Dead of Heart Disease, January 1947

Group	No. of Patients	Ages at Death	Average Age	Years Aortic Insufficiency Known
I	1	81	81	8
II	1	60	60	5
III	6	42–73	62.8	2–8
Total	8*	82–81	63.1	2–8

* All were white males.

for five years. In all the cases that died in failure, the heart size was markedly increased. All but three patients who died were in the seventh and eighth decades.

DISCUSSION

In the previous study from this clinic, it appeared that the length of the asymptomatic phase might be measured in years rather than months. The present study confirms the assumption that the asymptomatic phase of this valvular disease is measured in years (two to 10, average six years), and that even after the onset of the symptomatic phase the patients may maintain compensation, continue to work, and live two to 14 years (average 5.6 years).

The data presented in this study represent the survival time from the discovery of the aortic insufficiency to the time of death, or to the time the study was terminated. It is reasonable to assume that in many patients the aortic insufficiency was unrecognized for months, perhaps years. In 32 of the series, the diagnosis was established at the time of the first visit to the clinic. Moreover, at the completion of the study, 30 (70 per cent) of the patients were still alive and in apparent good health, 12 (28 per cent) completely asymptomatic.

It is difficult to evaluate the factors responsible for the more favorable outlook in this series as compared to those previously reported by others.[5, 13] Some authors have suggested that heavy labor is detrimental; others say that sex and race play an important rôle. It is frequently stated that Negro males present the poorest prognosis.[13] It should be noted, therefore, that the present study included only one colored male and three colored females, and that none of the patients worked at heavy labor. Age may be another mitigating factor; the majority of the patients fall into the seventh and eighth decades. Restriction of activity in this period of life probably plays a beneficial rôle in the brighter prognostic picture. The average age of those who died in heart failure was 63.1 years. This suggests that the degenerative processes of old age were in some measure responsible for death. All the patients were followed closely, and congestive failure was treated as soon as detected, with digitalis and mercurial diuretics. With the exception of the six symptomatic patients who died in the first two years of the study, all received the prescribed anti-syphilitic treatment. The exact value of this therapy in prolonging life is also difficult to determine. Padget and Moore [14] report that anti-syphilitic therapy almost doubles the life span in aortic insufficiency. In the New York Hospital Syphilis Clinic, it has been customary to initiate treatment of cardiovascular syphilis with bismuth, and to introduce arsenicals several weeks later. A total of 100 injections of bismuth and 100 injections of arsenic has been arbitrarily chosen, and an effort has been made to continue the therapy without rest periods for four years.

Abnormal widening of the ascending aorta (as shown in table 3) was found in the three groups of patients, in some who died early, and again in some who remained completely asymptomatic throughout the entire period of the study. Although the significance of this finding in prognosis is not clear, it is certainly not always ominous. A low diastolic blood pressure, below 60 mm. of mercury, and, therefore, a low diastolic intra-aortic pressure, was found in only six of the patients in this study, four of whom have died. The significance of this finding, again, is not clear.

Appearance of cardiac decompensation in syphilitic aortic insufficiency is said to be an especially serious sign, as is precordial pain or the finding of an enlarged heart; moreover, digitalis is thought to be less effective than in cardiac disease of other etiology.[3, 5, 15] Nine of the patients were in congestive failure three to nine years previously, were treated with digitalis,

and were alive at the termination of the study. In those who had precordial pain, the survival period was even greater, an average of 9.4 years. It should be emphasized at this point that all but one of the surviving patients were well-compensated and carrying on their respective pursuits, as though they had never had cardiovascular syphilis. Moreover, six of these patients are actually symptomatically improved. Patients with "free" aortic regurgitation have previously been assigned a poor prognosis.[6] But again this was not borne out in the present study, as a "loud" murmur was frequently found in those who had remained asymptomatic throughout, and a "soft" murmur in many who had always been symptomatic.

Of all the tests available, a prolonged circulation time and a low diastolic blood pressure probably offer the best index of prognosis in syphilitic aortic insufficiency.

Summary

Forty-three patients with syphilitic aortic insufficiency which was intensively treated with bismuth and trivalent arsenicals were followed two to 16 years. In 27 of these individuals, determinations of cardiac efficiency were made in 1941 and again in 1946.

In the five and one-half year period of the investigation, the status of 20 of the 43 patients changed for the worse. In only six of the 18 asymptomatic patients, however, did symptoms develop. Thirteen of the whole group of 43 died, eight of heart disease. Seven had to be reclassified as symptomatic-on-questioning or frankly symptomatic.

At the termination of the study, all the 27 living patients but one were well-compensated despite the duration of their aortic insufficiency (six to 12 years) and were able to continue their usual pursuits. Twelve of the 27 remained completely asymptomatic.

Eleven of the symptomatic patients were maintained on digitalis for two to six years with improvement in compensation. Six of the symptomatic patients actually improved during the period of observation.

Conclusions

1. Syphilitic aortic insufficiency may be characterized by an asymptomatic phase of at least two to 10 years.
2. A symptomatic phase usually occurs. This may last two to 14 years.
3. Cardiac failure may be as readily controlled with digitalis and mercurial diuretics as cardiac failure in other types of heart disease.
4. Prolonged circulation time and low diastolic blood pressure offer the best indices for prognosis.

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POST-PARTAL HEART DISEASE*

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The subject of heart disease complicated by pregnancy has been one of considerable interest for many years and a voluminous literature has been devoted to its discussion.[1, 2, 3] The reverse of this problem; namely, that of pregnancy complicated by heart disease of the usual etiological types,[4, 5] is an everyday one and certainly deserving of much consideration. However, that the puerperium may sometimes be complicated by a type of heart disease that bears a definite relationship to pregnancy, the puerperal period or both; that possesses a definite clinico-pathological character, and that features a prognosis quite different from the usual types of heart disease is not widely known. This is a separate entity from the so-called "physiologic gestatory heart disease" [6] and the cardiac failure secondary to toxemia of pregnancy [7] or activated glomerular nephritis.[8, 9, 10] "Physiologic gestatory heart disease" is merely the overworked heart of pregnancy, the result of increased cardiac output, increased blood volume,[12] increased velocity of blood flow and diaphragmatic elevation. These factors lead to the development of murmurs, usually systolic in time, changes in cardiac tones, gallop rhythm, pedal edema and roentgenologic evidence of cardiac enlargement. This picture is well known and offers no difficulty as a rule in its correct interpretation. The cardiac failure secondary to toxemia of pregnancy is the response to an acute hypertension according to White [13] and is characterized by its predilection for young primiparas, its occurrence in the last trimester of pregnancy, the associated preëclamptiform or eclamptic symptomatology and its dramatic response to therapeutic abortion. Glomerular nephritis, either the acute phase or the acute exacerbation of the chronic phase, quite commonly makes its appearance during pregnancy and may present mainly as a picture of myocardial failure. The complaints of headache, visual disturbances, weakness, pallor and pedal edema plus the hypertension and the "nephritic urine" aid in its diagnosis.

The type of heart disease to be discussed in this paper, termed by Hull,[14] "post-partal heart disease," is a quite distinct cardiac disease from the above mentioned types.

History

Although it is still far from being widely recognized and discussed, postpartum heart disease was undoubtedly referred to by Virchow [15] as long ago

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as 1870 in his discussion of "an idiopathic myocardial degeneration"; according to him, a not infrequent finding in women who died in the puerperium. Porak,[16] in 1880, in addition to corroborating Virchow's work, drew the sage conclusion that "this type of cardiac disease is more morbid than mortal," proving his clinical knowledge of its prognosis by this statement. Blacker,[17] in 1907, and Campbell,[18] in 1923, pointed out the occurrence of a non-valvular type of heart disease both in late pregnancy and the puerperium. Herrmann and King,[19] in 1930, described four cases of myocardial failure appearing during the puerperium which possessed no apparent histories or clinical features referable to the usual etiologic types of heart disease. Williams,[20] in 1933, using a large autopsied series for his information, made the statement that 1.5 per cent of cardiac deaths soon after pregnancy were the result of an idiopathic myocarditis. Since the above reports, more cases have been described and a characteristic clinical syndrome has been developed by Hull and Hafkesbring,[14] Gouley, MacMillan, and Bellet,[21] Musser, Sodeman and Turner,[22] and others.[23, 24]

Clinical Features

The earliest symptoms usually appear from between two to six weeks after parturition. The onset is, as a rule, insidious, early symptoms being pedal edema, dyspnea or cough. This chronicity of onset is merely the rule, as an acute attack of left ventricular failure may herald the appearance of cardiac decompensation. Occasionally, in retrospect, one may connect these symptoms of cardiac failure with vague complaints by the patient of dyspnea, ankle edema and palpitations in the last few weeks of pregnancy which apparently were relieved by delivery. Where the symptoms and signs of pregnancy end and those of post-partal heart disease begin is indeed a difficult clinical decision, but it is known that *true* cardiac failure with its many characteristic signs and symptoms never appears in the condition under discussion until, at earliest, a week or two weeks post-partum. Edema gradually increases in severity, reaching extreme proportions, and effusions in the serous cavities are frequent. As with any myocarditis, there are found cardiac enlargement, usually marked, and a rapid rate, but nearly always regular rhythm. Diastolic gallop rhythm, small volume pulse and anasarca are nearly always to be found. Usually the diastolic blood pressure is elevated and frequently both systolic and diastolic pressures. Laboratory data are non-specific, but quite uniform in some respects. Almost invariably upon fluoroscopic examination of the heart, a grossly dilated heart is seen with no selective enlargement of any particular chamber, only a generalized dilatation. The electrocardiogram is usually abnormal but with no uniform pattern. One point of value in differential diagnosis has suggested itself to the author and is offered purely as a personal observation; namely, that the electrocardiographic changes do not vary from day to day to the extent that one finds in the myocarditis of rheumatic fever, Fiedler's

myocarditis, trichinosis and so forth. The urinalysis varies in no degree from that found in any type of congestive failure and the hemogram and blood chemistry are within normal limits.

One characteristic of post-partal heart disease is the refractoriness to treatment. Compensation is usually much more difficult to attain than in the recognized etiological types of heart disease. Hull has made the observation that morphine and paracenteses afford the greatest relief. This is quite a paradox, considering the promising long term prognosis that these cases usually possess. With the usual cardiac treatment, however, these patients gradually lose their edema and dyspnea. Their gallop rhythm disappears and the blood pressure falls to normal limits. They usually require at least a week and usually much longer, however, to achieve this. In the several series reported from Charity Hospital, it has been noticed that this condition occurs much more frequently in the colored race than in the white race, that it follows the first pregnancy more often than subsequent pregnancies, that the incidence of toxemia of pregnancy and twin births in the patients is higher than usual and that a poor dietary history is often obtained. Embolic phenomena occur with striking frequency.[21, 23] As high as 25 per cent of the patients in Hull and Hidden's [23] series suffered embolic complications. Pulmonary embolism occurs more frequently than peripheral embolism and postmortem examinations have shown the source of these emboli to be from stasis thrombi in the ventricles. An important clinical feature of this type of myocarditis is the good prognosis. Even though recurrences of failure may develop with subsequent pregnancies (Case 1), the large majority of these patients make a complete and final recovery.

Case Reports

Case 1. E. W., a colored female, age 32 years, was first admitted to Charity Hospital in New Orleans on September 9, 1941, with the chief complaint of shortness of breath and swollen ankles of one week's duration.

Present Illness: In 1935, the patient became pregnant, and early in the course of the pregnancy (Case 3 of Gouley, et al.[21]) she began to have headaches, scotomata, dizzy spells, pedal edema and vomiting. These symptoms soon disappeared and there was no interruption of or complication of this pregnancy.

In November of 1940, she again became pregnant, and was delivered by a midwife, uneventfully, in July of 1941. However, during the latter part of this second pregnancy, she again had occasional pedal edema, shortness of breath and a "heavy" sensation in the chest following exertion. During the latter part of August, the patient was awakened at night by a severe pain under the left breast followed soon thereafter by dyspnea, coughing and pedal edema. These symptoms became worse and forced her to come to Charity Hospital.

Medical History: No history of rheumatic fever, chorea, diphtheria, scarlet fever or syphilis could be obtained.

Family History: The mother died of heart disease but the patient did not know at what age. The cause of the father's death was unknown. There were no other siblings.

Social History: The patient's diet consisted mainly of beans and her meals did not include eggs or milk. The patient seldom ate meat, having it only about once a week.

Physical Examination: Blood pressure 170 mm. Hg systolic and 128 diastolic. Temperature 99°. Pulse 90. Respirations 60.

General: A colored female of about 30 years of age who appeared orthopneic. She was sweating profusely and appeared anxious.

Head: Negative. Skull negative. Oral mucosae appeared pale and cyanotic. Fundi appeared normal upon ophthalmoscopic examination. There was no glossitis or cheilosis.

Neck: Moderate venous engorgement was present. The thyroid was not palpable.

Thorax: Respirations were 60 per minute and labored. On auscultation, crackling râles were heard over both lower lung fields posteriorly and dullness to percussion was found at both lung bases. Breath sounds and voice sounds were diminished.

Heart: The apex beat was diffuse. The heart was enlarged to the anterior axillary line in the fifth left interspace. The apical and radial rates were 96 per minute. The rhythm was regular. A protodiastolic sound was demonstrated at the apex. Soft systolic murmurs were heard at the apex and base. These were not transmitted to any great extent.

Abdomen: The liver could be palpated seven centimeters below the costal margin. The spleen and kidneys were not palpable.

Extremities: Two-plus pitting edema of the lower extremities to the knee level was found.

Reflexes: Physiological. No calf pain on pressure.

Genitalia: Normal adult female.

Rectal: Negative.

The impression on this admission was of hypertensive cardiovascular disease with congestive failure and malnutrition.

Course: Morphine, atropine and nasal oxygen were immediately administered to the patient and rapid digitalization was instituted. Diuretics were also given. A venesection was performed and 375 c.c. of blood were removed. The patient showed marked improvement following the phlebotomy, with decreased dyspnea and some alleviation of her other symptoms.

A roentgenogram of the chest, taken on the same day (September 9, 1941), showed cardiac enlargement and congestion of the bases. There was prominence of the lung markings. A blood count on the day of admission showed 4,200,000 red blood cells, hemoglobin 80 per cent. Upon urine analysis, the urine was found to be yellow with an acid reaction. The specific gravity was 1.030. There was a two-plus albumin reaction and the test for sugar was negative. On microscopic examination occasional pus cells and red blood cells per high power field were found. Numerous finely granular casts and hyaline casts were seen. The Kline and Kolmer tests were negative and the serum proteins were 6.76 grams per cent. An electrocardiogram on September 10, 1941 was interpreted as follows: "PR .13. QRS .08. Auricular rate 133. Ventricular rate 133. QRS of low amplitude. T_1 and T_4 inverted. R_1 slurred, S_3 notched. Definite evidence of myocardial disease."

On the third hospital day the patient's condition had markedly improved. The râles and edema had subsided to a great extent and there was only slight dyspnea. The blood pressure in the right arm was 190 mm. Hg systolic and 120 diastolic. The patient's blood pressure on September 15, three days later, was 130 systolic and 82 diastolic in the right arm. The following day no residua of the patient's cardiac failure was evident and she was allowed gradually to increase her activities. The digitalis and other medications were discontinued because of the possibility that this

case was one of post-partal heart disease. An electrocardiogram taken on September 18 still showed electrocardiographic evidence of myocardial disease. There was little or no change from the tracing taken on September 10, eight days previously.

The patient's blood pressure in the right arm on September 18 was 130 systolic and 92 diastolic.

Another roentgenogram of the chest made on the eleventh hospital day, September 20, showed slight enlargement of the cardiac shadow. The congestion in the bases seen in the film made on the day of admission had cleared completely.

The patient's blood pressure, when taken on September 21, was 110 systolic and 80 diastolic. A urinalysis performed on the same day revealed the color to be yellow, the reaction acid, and the specific gravity to be 1.020. There was a two-plus albumin reaction with a negative sugar reaction. On microscopic study, occasional granular casts were found to be present. The urea clearance was reported as 85 per cent the first hour and 80 per cent the second hour.

The report of a blood study done on September 23 showed 65 per cent hemoglobin and a red blood cell count of 3,900,000 per cubic millimeter. The total white and differential white counts were within normal limits. The patient's blood pressure on September 24 was the same as on September 21; namely, 110 systolic and 80 diastolic. The patient was considered at this time to be completely compensated and discharge was contemplated. Four days later, just prior to discharge, the patient was found to have pulsus alternans and, upon discovery of this condition, digitalization and complete bed rest were ordered.

An electrocardiogram on September 29 was reported as follows: "Auricular rate 121. Ventricular 121. PR .12. QRS .085. Sinus tachycardia with left axis deviation. T_1, T_2, and T_4 inverted. Definite electrocardiographic evidence of myocardial disease. The changes from the electrocardiogram made on September 18 may have been due to digitalis. A sound record on September 29 showed a soft systolic and possibly a presystolic murmur at the apex with a soft systolic murmur at the base."

On the following day, September 30, a roentgenogram of the chest showed slight enlargement of the cardiac shadow. The lung fields were clear.

The patient's blood pressure recorded on October 2 was 132 systolic and 106 diastolic. The pulse rate was 90 per minute and pulsus alternans and protodiastolic gallop rhythm were present. On October 9, a roentgenogram of the chest revealed slight enlargement of the cardiac shadow, especially in the region of the left ventricle. The lung fields were clear. The gallop rhythm and pulsus alternans had disappeared during this week. On October 17 physical examination revealed no evidence of congestive failure and two days later she was discharged to the Special Medicine Clinic. The following information was recorded in this Clinic:

On November 8, 1941, there were negative findings on physical examination. Digitalis was discontinued at this time. The patient was next seen on December 6, at which time there were still no abnormal findings.

The patient did not return to the Clinic until January 17, 1942, when she reported that she had a persistent cough. This was apparently the result of an upper respiratory infection. The blood pressure was 130 systolic and 92 diastolic. Codeine and elixir of terpene hydrate were prescribed for her.

The physical findings were still normal on March 28, 1942, her next visit. The patient came to the Clinic on July 11 and complained of dyspnea, substernal pain, vertigo, and nervousness. At this time, again, the physical examination seemed to be without significance. An electrocardiogram on this day was interpreted as, "definite evidence of myocardial disease with no significant change from previous electrocardiograms." On September 15, 1942, when the patient came to the Clinic, she had suffered for three weeks from shortness of breath, paroxysmal nocturnal dyspnea and pedal edema. Upon physical examination, cardiac enlargement was present with

ectopic beats and a soft systolic murmur at the apex. On fluoroscopy, marked left ventricular enlargement was demonstrated. She was immediately digitalized and given instructions regarding restriction of salt and fluids. On October 6, the patient came in with a chief complaint of dizzy spells every two to three hours when she was up and about. Cardiac enlargement was again noted on physical examination. There was a diffuse apex beat and a systolic murmur at the apex and base. The blood pressure was 120 systolic and 60 diastolic, with pulsus alternans, so the patient was admitted for observation.

Second Admission: The patient's chief complaints on her second admission were shortness of breath and edema of the ankles of two weeks' duration. Again the patient was placed on a cardiac regime. Following this she achieved a slow but uneventful recovery. The patient was then, again, discharged to the Special Medicine Clinic. She was later admitted to the hospital on March 27, 1945 for gynecological surgery. She withstood this uneventfully and was last seen in July, 1945, in the Special Medicine Clinic, at which time she presented no signs or symptoms of heart disease. In reply to a postcard sent to her in August of 1945, she stated "that she was in good health and was taking no medicine."

Case 2. L. M., a 31 year old colored female, was admitted to the Surgery Service on November 17, 1941, with a diagnosis of incarcerated para-umbilical hernia. In the history, it was brought out that following the birth of her first child in December, 1940, she suffered from progressive cardiac failure. Pedal edema, dyspnea and orthopnea were noticed during the last month of pregnancy and, following delivery, they became more pronounced. This condition progressed until she consulted her local physician. Under his treatment, she rapidly became symptom-free and remained so up until the time of this admission, except for slight dyspnea and occasional pedal edema. She was taking no digitalis at the time of admission.

Past History: The patient reported no history of rheumatic fever, "inflammatory rheumatism," repeated sore throats or syphilis. There was no history of pyelitis or Bright's disease. Symptoms of pellagra, beri-beri and other nutritional deficiency states were denied.

Family History: This was of no significance.

Social History: The patient is a housewife who gave a good dietary history. She does not use alcohol or habit-forming drugs, and she lives in clean surroundings.

Physical Examination: Blood pressure 134 systolic and 118 diastolic. Pulse rate 125. Respirations 28. Temperature 98.4°.

General: The patient was a well developed, well nourished colored female, appearing mildly dyspneic and somewhat apprehensive. The complexion was sallow.

Head: There was slight edema of the eyelids. The conjunctivae were pale. Fundi were normal in appearance.

Neck: Slightly engorged and pulsating neck veins were noted. The thyroid was not palpable.

Thorax: Fine, moist, inspiratory râles were heard at both bases posteriorly.

Heart: The point of maximal impulse was in the anterior axillary line in the sixth left intercostal space. The apex beat was forceful and diffuse. Enlargement to the right and left was found upon percussion. A blowing systolic murmur, loudest at the apex and transmitted to the left axillary region, was demonstrated. A diastolic gallop rhythm was present. The apex and radial rates were both 120 per minute and regular.

Abdomen: There was evident distention of the abdomen. Questionable shifting dullness and fluid wave were elicited. A para-umbilical hernia, four centimeters in diameter and easily reducible, was present. Liver dullness to three centimeters below the right costal margin was found. There was slight sacral edema.

Extremities: There was a two-plus pitting edema of the lower extremities to the knees.

Genitalia: Normal female multipara.

Rectal: Negative.

Neurological: The reflexes were physiologic and there were no abnormal ones present.

Course: On November 18, one day following admission, the patient was seized with a sudden attack of dyspnea and severe pain in the left chest. On physical examination, signs of left ventricular failure were found and the patient was immediately administered morphine, atropine, oxygen and intravenous digitalis. She was then transferred to a medical ward where complete cardiac care was instituted.

At that time a hemogram revealed 4,500,000 red blood cells with 90 per cent hemoglobin. There was a white blood cell count of 4,600 with a normal differential. On this same day a urinalysis was performed. The urine was brown in color and there was an acid reaction. The specific gravity was 1.030. There was a four-plus albumin reaction and a negative test for sugar. The sediment showed six to eight white blood cells and two to three red blood cells per high power field. Occasional hyaline casts were seen.

Blood chemistry, also done at this time, demonstrated the following: Urea nitrogen 18.2 mg. per cent, glucose 105 mg. per cent, Kline and Kolmer negative. An electrocardiogram, interpreted by Dr. James L. Gouaux, was reported as: "Auricular rate 110 per minute. Ventricular rate 110 per minute. PR interval 0.15 second. QRS interval 0.08 second. Sinus tachycardia, QRS complexes of low amplitude, all T waves low, T_4 notched. Strongly suggestive of myocardial disease."

A roentgenogram of the chest revealed cardiac enlargement and pulmonary congestion. Fluoroscopy of the chest revealed marked cardiac enlargement, involving all of the chambers. Pulsations were markedly diminished.

The patient responded gradually to her cardiac management with a slow disappearance of the edema, ascites, dyspnea and pulmonary engorgement. Her urine findings reverted to normal and a urea clearance test done on November 30, revealed 100 per cent clearance. An eye ground examination again revealed normal fundi. Her blood pressure was found to be 126 systolic and 86 diastolic on December 18, and 120 systolic and 70 diastolic on December 19. Cardiac fluoroscopy on December 19 revealed no evidence of the previous enlargement. A low grade fever developed on December 20, but, due to the fact that the patient left the hospital against orders, her course could not be followed for evaluation.

In answer to a postcard sent to the patient, she stated that she was "taking no medicine and feeling fine," except for slight occasional symptoms resulting from the hernia.

Case 3. D. R., a 21 year old colored female, entered Charity Hospital on March 28, 1944, with the chief complaint of "bad heart and bad kidneys."

Present Illness: This dated back to January 21, 1944, when the patient delivered, spontaneously, a seventh month, premature infant, which died soon after birth. During the last month of this pregnancy, which was her first, she had noticed ankle edema, blurred vision and dizziness. She was also told that she had "high blood pressure" at this time. These signs and symptoms disappeared after delivery, but two or three weeks following delivery, she was again troubled with ankle edema. About this same time, she suffered from a "pneumonia," characterized by sudden onset of chest pain, grossly bloody sputum, severe dyspnea and a rapid (four-day) response to sulfadiazine. The ankle edema persisted, however, and gradually dyspnea progressing to orthopnea developed.

Past History: No history of lues, rheumatic fever, scarlet fever, diphtheria, pyelitis or nephritis could be obtained. Symptom complexes resembling trichinosis were denied and there was no hypertensive history except during the period prior to delivery.

Review of Systems: Essentially as stated above.

Social History: A fairly good dietary history was obtained, with no particular deficiency in meat, eggs and milk.

Physical Examination: Temperature 99°. Respirations 30. Pulse rate 120. Blood pressure 115 systolic and 95 diastolic.

General: A well developed, well nourished, colored female of about the stated age, who was in severe respiratory difficulty and presented generalized anasarca.

Head: Negative. Eye grounds were normal. No glossitis or cheilosis present.

Neck: The thyroid was not palpable. Venous engorgement was evident and quite severe.

Chest: The chest was symmetrical with no tendency to lag on either side. Dullness to percussion, impaired tactile fremitus and absent breath sounds were demonstrated over the bases of both lungs posteriorly. The point of maximal impulse was in the sixth left intercostal space in the anterior axillary line and quite diffuse in nature. The left border was percussed 12.5 centimeters from the midsternal line. Upon auscultation, a loud protodiastolic gallop sound was heard at the apex. A blowing systolic murmur, not widely transmitted, was also heard at the apex.

Abdomen: The abdomen was visibly distended and both shifting dullness and a fluid wave were demonstrated. The liver was palpated three centimeters below the right costal margin. The spleen and kidneys were not palpable. Sacral edema was present.

Extremities: Three-plus pitting edema of both legs into the thighs. Venous pressure performed in the antecubital fossa area was 230 millimeters of water.

Neurological: Normal reflexes present.

The laboratory work was as follows: The urine was acid in reaction, concentrated to 1.024, and gave a negative reaction for sugar. There was one-plus albumin. The sediment examination was quite normal. The blood picture revealed a mild hypochromic, microcytic anemia with a normal total white and differential white count. The carbon dioxide combining power was 40 volumes per cent; the blood urea nitrogen was 11.1 mg. per cent, and the cholesterol was 180 mg. per cent. The Kline and Kolmer tests were negative.

A roentgenogram of the chest showed marked enlargement of the cardiac shadow to the left and right, with fluid at both bases and passive congestion. The electrocardiogram was read as follows: "Auricular rate 98 per minute. Ventricular rate 98 per minute. PR .16 second. QRS .08 second. T-waves of low amplitude in all leads. Suggestive evidence of myocardial disease."

Course: The patient was immediately placed upon a full cardiac regime including digitalis, salt restriction and diuretics and, in addition, was given large doses of the vitamin B complex, both orally and parenterally. Blood cultures were taken on five occasions because of a low grade fever, but all were reported as showing no growth. Repeated urines revealed no significant changes. Repeated electrocardiogram showed no changes from the previously reported one. A slow but gradual response to medication began at the end of the first week in the ward, but thoracentesis was finally resorted to in order to remove the bilateral pleural effusions. Ankle edema, râles, dyspnea and ascites gradually disappeared during the second week. The blood pressure was recorded on April 4, April 5, and April 10, 1944, and upon these three occasions it was found to be 120 systolic and 75 diastolic. The gallop rhythm persisted into the third week before disappearing. Thirty-five pounds of weight were lost in these three weeks. The patient was discharged on April 16, 1944, and followed in the Medicine Clinic, where, on June 22, 1944, digitalis was withdrawn. Up to the present time (October 16, 1945) she writes that she has had no more difficulty.

Case 4. E. M. N., a colored female, 21 years of age, was admitted on May 29, 1944, with the complaints of abdominal swelling, swollen ankles and shortness of breath.

Present Illness: The patient was delivered of her first child in March, 1944, following an uneventful pregnancy. About two weeks previous to admission, she noticed the appearance of swollen ankles, which gradually became worse. At about this same time, she was aware of a gain in weight and dyspnea upon exertion. This progressed to dyspnea at rest and abdominal distention was first perceived at about this time. She consulted her local physician, but failed to gain any relief. Orthopnea prevented her from restful sleep and one episode of nocturnal dyspnea at this time compelled her entrance into Charity Hospital.

Review of Symptoms: Essentially negative except as listed above.

Past History: The patient denied by name or symptomatology, rheumatic fever, chorea, syphilis, kidney disease, hypertension, or recent infection of any type.

Social History: The patient's diet was quite adequate with no shortages of milk, meat or eggs.

Physical Examination: Blood pressure 160 systolic and 110 diastolic. Pulse rate 160 per minute. Respirations 24 per minute. Temperature 98.8° (oral).

General: A well developed, well nourished, colored female of about 20 years of age who was moderately dyspneic and presented evident abdominal enlargement.

Head: Negative. Skull negative. Sclerae clear, no exophthalmos. Funduscopic examination was negative except for questionable arteriolar spasm. Hearing range and otoscopic examination were negative. Oral mucosa slightly pale. Severe dental caries were present. There were no oral or labial lesions suggesting vitamin deficiency and no glossitis present.

Neck: Thyroid was not palpable. Evident venous engorgement was present.

Thorax: Fine, moist râles were heard at both lung bases posteriorly.

Heart: The heart was enlarged to percussion, the point of maximum impulse being in the left anterior axillary line in the sixth interspace. Apical and radial rates were 100 per minute and quite regular. A Grade II systolic murmur and a diastolic gallop sound were present at the apex.

Abdomen: There was marked distention of the abdomen and a fluid wave was elicited. The liver was quite difficult to palpate, but it was thought to be three or four centimeters below the right costal margin.

Extremities: Four-plus pitting edema of the legs to the knees was present. The reflexes were normal and there was no hypesthesia or calf tenderness elicited.

Neurological: Normal reflexes and no pathologic reflexes present. Pelvic and rectal examinations were negative.

Course: The patient was immediately placed upon a cardiac regimen, i.e., rapid digitalization, ammonium chloride, low salt diet and Mercupurin, etc. A roentgenogram the day of admission revealed marked enlargement of the cardiac shadow and passive congestion. Blood chemistry, serology, urinalysis and complete blood study were within normal limits. The electrocardiogram on May 29, revealed the following: "PR 0.16. QRS .08. Auricular and ventricular rate 104 per minute. QT interval definitely prolonged, T_4 inverted. The circulation time (Decholin) from arm to tongue was 19 seconds and the venous pressure was 190 millimeters of water."

The patient showed a poor response to therapy but slowly regained compensation with the aid of two abdominal paracenteses and large amounts of ammonium chloride and Mercupurin. The blood pressure on June 1 was 150 systolic and 100 diastolic, on June 4, 135 systolic and 85 diastolic, on June 11, 120 systolic and 80 diastolic. A second roentgenogram of the chest on June 14 was reported as showing slight increase in lung markings, but otherwise normal. Venous pressure and circulation time were normal on this date and, clinically, the patient was compensated. An electrocardiogram on June 16 was unchanged from the previous one on May 29. Digitalis was discontinued at this time and on June 18 the patient was discharged to Medicine Clinic for weekly follow-ups. Up to the present date (September, 1945) she has progressed uneventfully, without digitalis, diuretics or salt restriction.

Pathology: The characteristic gross and microscopic pathology in this unusual type of heart disease is not clearly delineated or defined as yet in the minds of some pathologists. However, it features enough consistent changes to be regarded as quite distinct. Upon gross examination, the heart shows generalized dilatation with only slight hypertrophy evident. The epicardium is usually smooth and glistening and the muscle pale, grayish-brown in color, soft and mottled by congestion. Antemortem thrombi are frequently found enmeshed in the *trabeculae carneae*. The coronary arteries are patulous throughout with smooth intimal surfaces.

Microscopically, the pathology is characterized by focal lesions, only occasionally coalescing to become conglomerate and diffuse. These focal lesions present marked parenchymatous degeneration with irregularly sacculated muscle fibers, "wavy" in appearance because of cytoplasmic loss. Necrotic foci are numerous with varying degrees of cellular infiltration, chiefly lymphocytic, but with occasional neutrophiles or eosinophiles. A much larger cell with cuboid or oblong nuclei is usually present. These are thought to be the residual nuclei of the degenerated muscle, surrounded by necrotic sarcoplasm. Occasionally, these nuclei may be seen in compact, parallel rows. Hemorrhage into the necrotic areas is frequent. There is no hydropic degeneration of the muscle fibers, eosinophilic infiltration or interstitial edema. Occasionally one sees areas in which the focal lesions have been invaded by fibroblasts and pseudo-giant cells, with replacement of the myocardial nuclei, only acellular scars remaining.

Pathogenesis

The relationship of pregnancy and the puerperium to this type of heart disease at once raises some interesting questions. Is this condition an atypical hypertensive state stemming from an activated glomerulo-nephritis? The blood pressure readings in the large majority of these patients reveal a mild hypertension. Heart weights at necropsy usually show a moderate increase over normal. Whether this increase in heart weight was due to hypertrophy alone and not to the associated degenerative and edematous character of the pathology is an undecided point. Pathological examination of the kidneys may at times reveal moderate arteriolar sclerosis, areas of septic infarction or simply a congestive nephritis, but the typical features of a glomerulo-nephritis are absent. Pertinent histories, typical urinalyses and compatible clinical features of glomerulo-nephritis have been conspicuous by their absence. True, in some of the cases reported by Sodeman,[6] a clinical picture and urinalysis compatible with that of acute hemorrhagic glomerulo-nephritis was reported, but he divides these postpartal syndromes into a nephritic and a non-nephritic one, confirmed by Addis counts. Musser, Sodeman and Turner,[22] in an earlier article, also divided these two puerperal complications into these same two groups. In their cases, the nephritic

group was without evidence of disease until the puerperal period and developed within a week postpartum signs of sepsis followed in two to three weeks by typical acute hemorrhagic glomerulo-nephritis. They consider this sepsis as a streptococcal puerperal infection with the development of a sensitized state, and the subsequent nephritis following the two to three weeks latent period, the same mechanism as postulated for all acute hemorrhagic glomerulo-nephritis. Their non-nephritic cases showed little evidence of heart disease during pregnancy but developed typical congestive failure two to three weeks post-partum. It is true, however, that the heart failure of acute nephritis at times may show few or no urinary abnormalities [18] but usually hematuria is quite constant.[3] Acute glomerulo-nephritis can be ruled out on the above features in the large majority of cases.

As mentioned in the introduction of this article, toxemia of pregnancy may be complicated by myocardial failure,[13] again, as in glomerulo-nephritis, the result of an acute hypertension. Toxemia of pregnancy bears some resemblance to post-partal myocarditis in that both occur most frequently in young primiparas, especially the negro primipara, and in multiple pregnancies. The fact that toxemia of pregnancy never occurs later than approximately one week post-partally immediately militates against the direct relationship of these two conditions.

Is this condition merely the myocardial failure of an essential hypertensive state? Admittedly, the positive differentiation from post-partum heart disease is extremely difficult, sometimes impossible. Both conditions feature diastolic hypertension and it is obviously impossible in some cases to determine the duration of this hypertension. The absence of a history of hypertension or of hypertensive heart disease prior to pregnancy, absence of signs of left ventricular hypertrophy in the electrocardiogram, the return of cardiac size and the blood pressure to normal limits, and the younger age group would all tend to cast considerable doubt as to the identity of this condition with essential hypertensive heart disease. Funduscopic examinations in these reported cases revealed signs of a chronic hypertension and the kidney function was well within normal limits, considering the congestive state. Renal arteriosclerosis is usually absent at autopsy [21] and when present is of a mild nature, indicating a hypertension of short duration. Moreover, the reported histopathology of the cardiac muscle is certainly not that of chronic hypertension.

Hull [14] makes the statement that the clinical pictures of cardiac beri-beri and post-partal heart disease are identical if one disregards the neurological features of beri-beri heart disease. White,[13, 25] however, indicates that in beri-beri heart disease the neurological phenomena are occasionally absent, the avitaminosis being manifested entirely as pure cardiac failure. Undoubtedly, some of the cases reported by Hull [14] and Gouley et al.[21] and one of the cases reported in this paper had a grossly deficient diet during pregnancy. Thus, it would seem as though post-partal heart disease could at

least be a conditioned variant of beri-beri heart disease. If so, why the refractoriness to specific vitamin therapy and why its occurrence post-partum when vitamin requirements would certainly tend to be lowered? Again, why the difference in pathology in the two conditions? True, fragmentation of the muscle fibers is common to both conditions, but the hyaline and fatty degeneration found in beri-beri heart [25] has not been reported in post-partal heart disease. Until these questions are answered, these two conditions must be considered as distinct clinico-pathological entities.

It is recognized that rheumatic heart disease may present in varied clinical pictures, but the absence of a rheumatic history, the distinct differences in the clinical course, the absence of typical murmurs and, above all, the different pathological features would tend to rule out such a diagnosis.

The possibility that post-partum heart disease might be related to an infectious process was first entertained by Virchow.[15] Gouley et al.[21] have discussed the causal influences of infection only to reject them. With the exception of one case, none of their patients presented any evidences of infection and necropsy only verified this clinical opinion. This one case died with a *Staphylococcus aureus* septicemia resulting from a stubborn bed sore, the result of three months of cardiac decompensation and obviously not its cause.

The clinical picture and also the gross appearance at autopsy resembled that rare form of myocarditis, usually given the name, "Fiedler's myocarditis." [26, 27] Most authorities consider this to possess an infectious etiology, but, in view of the varied precipitating and accompanying conditions associated with it, this opinion must be treated with considerable doubt. The pathology of this disease is usually reported as chiefly interstitial, but some cases revealed an associated parenchymal involvement with dissolution of the myocardial substance and the appearance of "myogenous" cells.[21] Saphir [26] has stated that two distinct types of myocarditis have been described pathologically for Fiedler's myocarditis, one a granulomatous and the other a diffuse inflammatory process. Obviously, in the light of such a vague pathological state, post-partum myocarditis could easily be mistaken by the pathologist for Fiedler's myocarditis. However, as far as can be ascertained, no reference has ever been made to pregnancy or the puerperium as having any bearing on the clinical course or possible etiologic relationship to Fiedler's myocarditis. It is worth reminder, however, that in view of the varied precipitating causes of Fiedler's myocarditis, pregnancy and the puerperium could act in a similar manner. Indeed, the exact clinical and pathological picture of post-partal heart disease has been reported in males [28] following upper respiratory infections. Eventually, as familiarity with the clinico-pathological picture is gained, all of these vague forms of myocarditis may be recognized as equivalents varying only in their predisposing and precipitating factors and possessing one of several types of recognized pathology.

TREATMENT

Although there is usually a response to the measures used commonly in the treatment of heart failure, it is not a striking one. Recovery is measured in terms of weeks and, in some cases, months, differing somewhat from the cardiac failure due to the usual etiological types of heart disease. It is hardly justifiable, nevertheless, to omit any detail of a vigorous therapeutic regime. Digitalis should be used to the full limit of efficiency and should be supplemented by the mercurial diuretics, and by salt and water restriction. Mechanical removal of fluid collections is usually more efficacious than the mercurial diuretics, since, for some reason, these patients respond poorly to the latter. Oxygen and Demerol injections are indicated during the acute attacks of dyspnea, so frequent in this condition. Measures directed against any possible pathogenetic factors are justified and a diet high in vitamins and proteins supplemented with iron is a standardized procedure. Because of the possible relationship of post-partal heart disease to the sudden increase in activity following delivery,[6] rest in bed should continue for several weeks after all edema has subsided and resumption of normal activity should be gradual. The immediate outlook for these patients is good, as the large majority make a slow but uneventful recovery, but this condition may recur following subsequent pregnancies and the patient should be informed of this fact. Two such episodes of failure should certainly justify sterilization.

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HEREDITARY POLYCYSTIC KIDNEY *

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The condition of polycystic kidney is also known as cystic disease of the kidney, cystic degeneration or congenital polycystic kidneys. The disease has always created interest because of the enormous size these kidneys may attain. It is encountered in infants but appears most often between the fortieth and sixtieth years. This is clearly noted in table 2 of this study. It normally has been found to be more common in the female than the male; however, this study disclosed more males than females (table 1).

Table I

Progeny of Generation II No. 6 (2 Generations)

	Positive Male	Negative Male	Positive Female	Negative Female
Positive male produced	2	3	4	1
Negative male produced	1	2	0	2
Positive female produced	4	3	1	1
Total	7	8	5	4
	Total—Positive 12 and Negative 12			

Table II

Summary of Dead Positive Members in Generations II, III, IV

	20–30	30–40	40–50	50–60
Positive males	—	—	2	6
Positive females	1	—	2	2

Etiology

Several theories have been presented but this paper will deal only with the hereditary factor. The coöperation of the family was unsatisfactory in many instances; however, enough data were acquired to form a basis for determining the hereditary trait.

Hereditary Factor. A marked hereditary tendency has always been noted in polycystic kidneys. In this study of the hereditary trait only those members are considered positive about whom enough clinical data were acquired to justify the diagnosis. All other members have been considered negative. The progeny of Generation II No. 6 for two generations is considered as the basis for determining the hereditary trait because these individuals are advanced in years and a fairly definite evaluation of each case

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can be made. The summary of this group (table 1) shows a 1:1 ratio of males produced by positive parents. It also shows a 1:1 ratio of females produced by positive parents. Positive males produce positive and negative males and females. Positive females produce positive and negative males and females. Generation III No. 4 is considered negative and is known to have produced one positive son. The other members of this family are considered negative because the history is inadequate. The patient died at the age of 67 of a cerebral vascular accident, which is a common terminal event in case of polycystic kidneys. His advanced age, however, is against his having polycystic kidneys, although some have been known to reach 80 years of age.

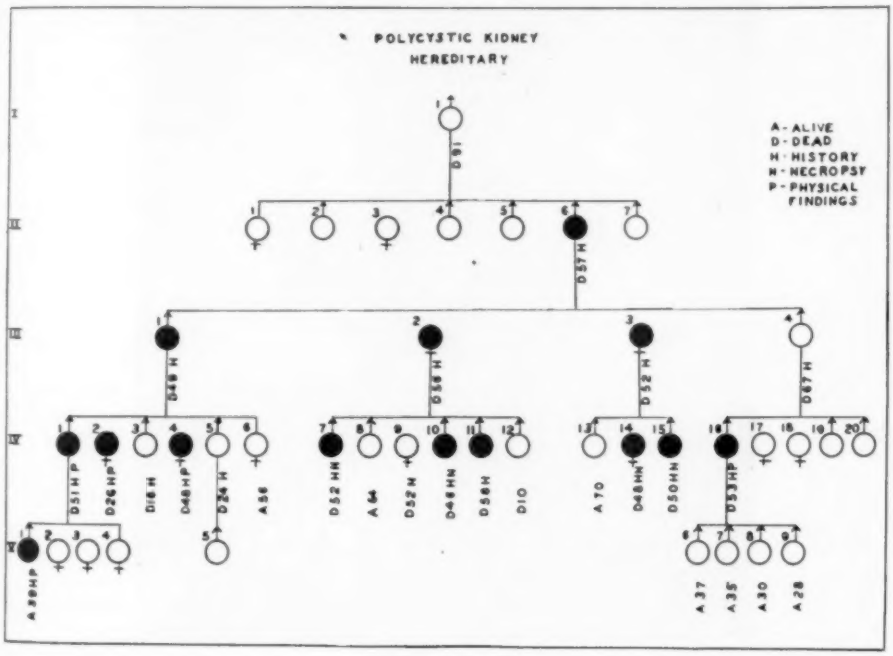

FIG. 1.

This summary shows a total of 12 positive and 12 negative members in two generations. It is concluded the trait is carried as a dominant factor and is not sex-linked.

Morbid Anatomy. Although unilateral polycystic kidneys have been noted, the examples presented in this study are bilateral. Figure 2 is a roentgenogram taken of a kidney removed at postmortem examination. The size, as indicated in inches, shows the organ a great deal larger than normal but the configuration of the kidney remains. The cysts have practically replaced the whole kidney. On gross examination no normal kidney parenchyma could be seen. Several autopsies were done and not reported in this case study.

Symptoms. The most important and first symptom is that of pain. The degree of pain varies from a heavy sensation at the onset to more severe pain as the kidney becomes larger. Hematuria is a very common finding in this group. It is known to occur during the second decade and to be one of the first symptoms. It is intermittent and profuse but caused no fatalities in this group. A palpable mass with progressive enlargement has been noted. This, however, was not as important a symptom as the pain and hematuria. Signs of chronic nephritis with albuminuria and hypertension were common.

FIG. 2. Roentgenogram of a polycystic kidney removed at autopsy.

Life Expectancy. A summary of the members of the family who have died is given in table 2. This summary shows that only one member of 13 died in the 40 to 60 age group. The average life span of all members in the above generations is above 47 years.

Treatment. There have been no operative procedures carried out on any members of this group. Treatment was chiefly palliative as symptoms appeared.

CASE REPORTS

Case 1, Generation II, No. 6, a white male born in 1831 and died in 1888 at 57 years of age. The patient came to America from England in about 1850. He had

the usual history of intermittent hematuria. It is well recognized by the family that this patient died of polycystic kidney.

Case 2, Generation III, No. 1, a white male born in 1854 and died in 1903 at 49 years of age. He died of polycystic kidney, having had intermittent hematuria and the symptoms known by the family to be associated with the disease.

Case 3, Generation III, No. 2, a white female born in 1855 and died in 1911 at 56 years of age of polycystic kidneys with the usual associated symptoms.

Case 4, Generation III, No. 3, a white female born in 1857 and died in 1909 of polycystic kidneys.

Case 5, Generation III, No. 4, a white male born in 1859 and died in 1923 at 67 years of age of a cerebral vascular accident. No autopsy was performed. The presence or absence of polycystic kidneys was not definitely known, and this case is considered as negative in figure 1. His one son definitely had and died of polycystic kidneys. This finding would lead one to think the patient had the disease and the presence of polycystic kidneys was probably the cause of hypertension, resulting in a cerebral vascular accident.

Case 6, Generation IV, No. 1, a white male, bank cashier, born in 1879 and died in 1930 at the age of 51 years. This patient was first examined two years before his death. The diagnosis at the time of admission was acute vesiculitis, vasitis, epididymitis and polycystic kidneys. His chief complaint was frequency of urination for one month's duration. After a tooth extraction the left testicle became red, swollen and excruciatingly painful. The patient noted gross hematuria and later pyuria. He had lost some weight and had not noted edema or palpitations.

Physical examination revealed a hard, swollen, tender, left testicle. The cord through the entire canal was swollen and tender. The left lobe of the prostate and vesicle were slightly enlarged and very tender. Examination of the abdomen showed a large mass in his left abdomen, reaching almost to the crest of the ilium. Roentgen examination of the abdomen showed an indefinite shadow which corresponded to the palpated mass and also a smaller mass on the right side. Fluoroscopy of the gastrointestinal tract showed the entire stomach to be displaced to the right.

The hemoglobin was 75 per cent, the red blood cell count 3,940,000 and the white blood cell count was 9,500. The blood urea nitrogen was 39.2 mg. per 100 c.c. The urinalysis revealed a specific gravity of 1.010 and was negative for albumin and sugar. Microscopic examination showed numerous white blood cells. The systolic blood pressure at times reached 190 mm. Hg and the diastolic was 90.

A diagnosis of polycystic kidneys, vesiculitis, vasitis, epididymitis and hypertension was made.

Case 7, Generation IV, No. 2, a white female born in 1882 and died in 1908. She had a definite history of polycystic kidney with the usual symptoms of hematuria and masses in the abdomen.

Case 8, Generation IV, No. 3, a white boy, killed in an accident at 16 years of age. He is considered normal in this study.

Case 9, Generation IV, No. 4, a white female, bookkeeper, born in 1887 and died in 1935 at 48 years of age. The patient was examined a few months before her death. She had first noted signs of kidney disease at 40 years of age, at which time she first noted intermittent hematuria which had continued until she was admitted for study. She had also noted palpable abdominal masses. The patient weighed 137 pounds. The skin was pale. The systolic blood pressure was 170 mm. Hg and the diastolic was 95. There were large masses palpable in both sides of the abdomen, the right larger than the left.

The hemoglobin was 48 per cent, the red blood cell count 2,320,000 and the white blood cell count 5,100. The blood urea nitrogen was 76 mg. per 100 c.c. The urine was grossly bloody.

Transfusions were given and the patient survived the episode only to die the same year some time after another hemorrhage.

A diagnosis of polycystic kidneys, hematuria and hypertension was made.

Case 10, Generation IV, No. 5, a white male, born in 1888 and died in 1912 at 24 years of age. He had no history of kidney disease. His son and grandson have shown no evidence of kidney disease.

Case 11, Generation IV, No. 6, a white female alive at 56 years with no history or physical findings of kidney disease.

Case 12, Generation IV, No. 7, a white male farmer born in 1879 and died in 1931 at 52 years of age. The patient had five living, well children. His chief complaints were dizziness, backache and dysuria. The patient had noted increasing symptoms of dizziness and nocturia for three to four weeks. He was aware of large masses in the right and left upper abdomen. He had previously had symptoms of nausea, vomiting, constipation, thirst, vertigo, chills, fever and diplopia. His backache had been present for years. He had marked urgency but could not void. He noted a knife-like pain which radiated from the lower abdomen to the bladder. He had noted no hematuria or discharge.

He was a large, pale, white male, 74 inches tall. His respirations were 20 per minute and the pulse was 84. Examination of the abdomen revealed a large, nodular, firm mass in each upper quadrant. There was a bulging in the left kidney region and tenderness over both kidney areas.

The hemoglobin was 79 per cent, the red blood cell count 4,290,000 and the white blood cell count 10,300. The blood urea was 49 mg. per 100 c.c.

The urine at no time had a specific gravity over 1.010. All examinations revealed a one-plus albumin and were otherwise negative.

The course was steadily downward and the patient died in coma.

The postmortem examination was limited to the abdomen. There was no free fluid in the abdominal cavity. The stomach was markedly dilated and extended below the umbilicus. The spleen was slightly enlarged. The liver and pancreas were normal.

About 6 cm. below the pylorus were two masses of gray, lobulated tissue in and under the serosa of the duodenum. Each mass measured 2.5 by 1 by 0.5 cm.

Microscopic section showed the masses to be made up of pancreatic tissue. One gave evidence of possible early malignant changes.

Both kidneys showed a polycystic involvement. No grossly normal tissue could be demonstrated. The left kidney measured 32 by 15 by 13 cm. and weighed 2,368 grams. The right kidney measured 30 by 17 by 10 cm. and weighed 2,358 grams.

Postmortem diagnosis: (1) Polycystic kidneys. (2) Accessory pancreatic tissue in the wall of the duodenum showing possible early malignancy. (3) Dilatation of the stomach.

Case 13, Generation IV, No. 8, a white male born in 1882, at present alive and well, showing no evidence of kidney disease.

Case 14, Generation IV, No. 9, a white female born in 1884 and died in 1936 at 52 years of age. The clinical diagnosis was acute pancreatitis and cholecystitis. An operation revealed extensive fat necrosis. An autopsy was performed and was limited to the abdomen. The pathological diagnosis was acute hemorrhagic pancreatitis with necrosis. The kidneys appeared to be normal.

Case 15, Generation IV, No. 10, white male, born in 1886 and died in 1932 at 46 years of age.

The patient entered the hospital with a diagnosis of convulsion, chronic interstitial nephritis, chronic myocarditis and arteriosclerosis.

The patient's history revealed a loss of weight during the past year. He had marked peripheral edema. The heart rate had been rapid and the blood pressure elevated.

The hemoglobin was 85 per cent, the red blood cells 4,440,000 and the white blood cell count 18,250 with a normal differential. The blood urea nitrogen was 18.2 mg. per 100 c.c. The urine was grossly bloody.

Diagnosis: Polycystic kidney, hypertension, hematuria. Clinical diagnosis as to cause of death was coronary thrombosis.

The postmortem examination was limited to the abdomen. All the organs appeared normal except the kidneys. Each kidney measured 25 by 15 by 12 cm. and was remarkably involved in a polycystic condition. No uninvolved kidney substance was seen on gross examination.

Case 16, Generation IV, No. 11, white male born in 1889 and died in 1939 at 50 years of age. A definite knowledge of polycystic kidney was present.

Case 17, Generation IV, No. 12, a white boy born in 1890 and died in 1900 of diphtheria.

Case 18, Generation IV, No. 13, a white male born in 1876, alive and well at present. He has shown no signs of polycystic kidneys.

Case 19, Generation IV, No. 14, a white female born in 1878 and died in 1926. The patient was first seen when she was 47 years of age, at which time a diagnosis was made of polycystic kidneys, secondary anemia and chronic myocarditis.

Her past history showed a cerebral vascular accident at 41 years of age, affecting the whole left side of the body. She had two living, well children at the time of this examination. She passed uneventfully through the menopause at 45 years of age.

Her chief complaints were swelling of the feet and dyspnea of six weeks' duration. During the past two weeks she had noted orthopnea. She had also noted swelling of the eyelids and a "lemon yellow pallor."

On physical examination she was a chronically ill white female with the important finding of an irregular abdomen. There was a large mass palpable in each upper quadrant extending below the crest of the ilium. The systolic blood pressure was 220 mm. of Hg and the diastolic 110. The hemoglobin was 45 per cent, the red blood count 2,320,000 and the white blood cell count 5,900, with 6 per cent eosinophiles. The 24 hour urine output averaged 1,580 c.c. The specific gravity never exceeded 1.010. There was a faint trace of albumin but otherwise the findings were negative.

The patient became steadily weaker and died at 52 years of age. Autopsy disclosed bilateral polycystic kidneys.

Case 20, Generation IV, No. 15, a white male born in 1883 and died in 1933 of polycystic kidneys.

The patient's chief complaints were a darker than usual urine of several days' duration. Urgency and frequency became so severe that he voided every five to ten minutes, at which time he passed small amounts of bloody urine. The urine stream was of normal size but would stop abruptly. After micturition he noted a severe pain radiating to the end of the penis. He had noted no blood clots.

His past history revealed similar symptoms eight years previously and also three months previously.

On physical examination he was markedly emaciated, 76 inches tall. The skin was dry and scaly. Abdominal examination disclosed a mass on each side extending from the kidney area to below the crest of the ilium.

The hemoglobin was 85 per cent, the red blood cell count 4,520,000 and the white blood cell count 8,200. The blood calcium was 10.0 mg. per 100 c.c. The creatinine 6.7. The blood sugar was 140 mg. per 100 c.c. The blood urea nitrogen on admission was 77 and increased to 230 mg. per cent during two months' hospitalization. Urinalysis showed a specific gravity of 1.010 and a one-plus albumin; and microscopically there were numerous red blood cells.

The patient developed a series of convulsions and died after two months' hospitalization.

Postmortem examination was limited to the abdomen. The gall-bladder was

distended to about 6 cm. in width and was 12 cm. in length. No stones were palpable. There was an old healed scar of a duodenal ulcer.

The left kidney extended the entire length of the left abdomen, lifted the diaphragm on that side and extended into the pelvis. It showed numerous cysts, some of which were hemorrhagic. The right kidney was cystic and hemorrhagic, but smaller than the left.

Autopsy diagnosis: (1) Polycystic kidneys. (2) Chronic cholecystitis. (3) Old healed duodenal ulcer. (4) Marked emaciation.

Case 21, Generation IV, No. 16, a white male, born in 1884 and died in 1937 at 53 years of age.

The patient was first seen three years before his death. He complained of nocturia, pain in the left side and palpable masses in the kidney areas. His temperature was 103.4° F., the systolic blood pressure was 134 mm. Hg and the diastolic was 74. The patient recovered from the episode.

The second admission was two years later at which time he complained of acute right upper abdominal pain. The patient was noted as being well developed and well nourished. His height was 70 inches and he weighed 185 pounds. There was tenderness and marked rigidity over the upper abdomen. There was a palpable mass in the area of the gall-bladder. There had been no previous attacks of gall-bladder trouble and no jaundice.

The white blood cell count was 38,400. The blood urea nitrogen ranged up to 79.8 mg. per cent. The urine examination showed a specific gravity of 1.011 and was negative for albumin, sugar and red cells.

Record of Operation: There was a mass in the right upper abdomen extending down to the umbilicus. On opening the abdomen a greatly enlarged and thickened gall-bladder was exposed. On excision of the gall-bladder, stones were observed. Stones were impacted in the cystic duct. Two greatly enlarged, polycystic kidneys were observed.

Diagnosis: (1) Acute and chronic cholecystitis with cholelithiasis. (2) Polycystic kidneys.

Case 22, Generation IV, Nos. 16, 17, 18, 19, were considered negative because data were inadequate.

Case 23, Generation V, No. 1, a white male, grocer, born in 1908. He was first observed in 1927 for a toxic thyroid, which was removed. The patient first noted symptoms referable to the kidneys in 1943. He has noted backache and hematuria, and masses in the abdomen. He has polycystic kidneys.

Case 24, Generation V, No. 6, a white male born in 1909. This patient has a dull, heavy sensation over the kidney areas, first noted in 1944. Repeated urinalyses have been negative. Intravenous pyelography has been negative.

This patient is considered negative in spite of suggestive symptoms.

Conclusions

1. A large family tree of polycystic kidney is presented.
2. The disease occurred through four generations.
3. The family tree is sufficiently large to serve as a basis for determining the type of hereditary trait.
4. The trait is carried as a dominant characteristic. It is not sex-linked.
5. The incidence is equal in males and females.
6. All but one member died between the ages of 40 and 60 years.
7. The onset of symptoms may be early and consist of backache, intermittent hematuria, palpable masses in the abdomen.
8. The kidneys reach enormous size, some weighing over 2,000 grams.
9. Histories and necropsy findings on several cases are presented.

CASE REPORTS

TOXICITY OF LARGE DOSES OF VITAMIN D (ERTRON) *

By Leroy Hyde, M.D., *Van Nuys, California* and Bernard Hyde, M.D., *Los Angeles, California*

Vitamin D has been used for its anti-rachitic properties, uneventfully, for about 20 years. Relatively recently, large doses of vitamin D have been used in the treatment of rheumatoid arthritis. Perhaps the primary reason for this has been the deluge of literature and advertising which has descended upon the medical profession, concerning the efficacy and low toxicity of an activated, heat-vaporized ergosterol made by the Whittier process. Both of these beliefs must be questioned.

Vitamin D

The rôle of vitamin D in the prevention and treatment of rickets is well known. The precise mode of action of this vitamin is not completely understood, but it is believed to increase the absorption of calcium and phosphorus from the bowel. Thus administration of vitamin D in rickets will convert a negative calcium balance into a positive one. When given in very high dosage, toxic effects may follow.

Large Doses of Vitamin D in Rheumatoid Arthritis

Numerous reports have appeared in the literature concerning this form of therapy. Several authors [1, 2] have reported favorably on the action of large doses of vitamin D (Ertron), mentioning the feeling of well-being of the patient, weight gain, and the return of the hemoglobin and red blood count to normal. Toxicity was minimized. Other observers have reported vitamin D to be of "little or no value in rheumatoid arthritis." [3, 4] Freyberg [5] states that "of the many newer forms of therapy for chronic arthritis, one of the most highly advertised is treatment with massive doses of vitamin D. . . . Benefit attributed to the vitamin occurs relatively seldom and usually is rather slight." Wagner [6] reported good results in six of 42 patients, using 200,000 to 300,000 units daily.

The efficacy of large doses of vitamin D in the treatment of rheumatoid arthritis is apparently unpredictable and very variable, differing greatly in the hands of different observers.

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Toxicity of Large Doses of Vitamin D

Numerous articles [3, 4, 5, 7-12] have appeared reporting the toxicity of large doses of irradiated ergosterol and other forms of vitamin D. As early as 1929 an editorial in the Journal of the American Medical Association [7] warned that irradiated ergosterol may cause impaired nutrition, weight loss, hypercalcemia, and abnormal calcium deposits in various tissues and organs. Abrams and Bauer [4] reported frequent toxic symptoms following the use of 200,000 USP units vitamin D daily in patients with rheumatoid arthritis. Freyberg [5] stated that in 16 per cent of patients receiving large doses of vitamin D the medication had to be discontinued because of toxicity. Another observer [10] reported that 18 of 31 arthritic patients treated with vitamin D (Ertron) developed toxic manifestations.

The more common symptoms of vitamin D intoxication [13, 14] are nausea, vomiting, anorexia, abdominal pain, diarrhea, weakness, lassitude, headache, pruritus, and polyuria. Renal calcification may inaugurate a train of urinary complaints. Brownish skin pigmentation has been noted.[15]

Metastatic calcification in various tissues and organs and death have been noted in animals [3, 4, 8, 12, 16, 17] and man.[7, 11, 12, 14, 17, 18, 19] Six patients have died and have been autopsied following hypervitaminosis D.[14, 17, 18, 19] Metastatic calcification was noted in all of these patients, and involved chiefly the kidneys, stomach, lungs, and arteries.

Case Report

E. V. S., 59 year old white male, was first seen on July 11, 1946, when he entered the hospital because of severe arthritic pain of most of the joints of the body, including fingers, wrists, elbows, shoulders, vertebrae, and knees, and because of the appearance of nodules on both arms. The past history revealed that the patient first noted arthritic pains of the neck 22 years ago. The arthritic pains spread slowly to other joints of the body, but did not involve the joints of the hands until 1940. One and one-half years before his present admission the patient developed massive swelling, redness, tenderness, and severe pain involving the joints of the fingers, both hands, and both wrists. There was also an exacerbation of the pain of both elbows, shoulders, and knees. The patient was placed on vitamin D (Ertron) 200,000 units a day, by his physician. This had no effect on his arthritis, but the patient noted anorexia and nausea one month after the onset of Ertron therapy. He had no abdominal pain and no vomiting. Three months after the onset of vitamin D therapy, he was told by his physician that he was anemic, and he received some unknown therapy for this. Six months after the onset of vitamin D treatment, he noted progression of his arthritis, both symptomatically (pain) and objectively (tenderness, limitation of motion, and increasing deformity), the development of nocturia and dysuria, and a 40 pound weight loss. The patient was hospitalized in August 1945, but his hospital physicians at that time apparently did not know that the patient was on vitamin D therapy. Pertinent findings from that hospital admission were as follows: Blood pressure 145 mm. of mercury systolic and 100 mm. diastolic. Examination of the head, eyes, ears, nose and throat were within normal limits. The lungs were clear. Examination of the heart was unremarkable. Examination of the abdomen gave negative findings. The prostate was moderately enlarged and firm. There was no generalized lymphadenopathy. There was limitation of motion of the neck with tenderness over the cervical vertebrae. There was tenderness and swelling of the phalangeal joints of the fingers of both hands. Laboratory work included an electrocardiogram which was normal except for

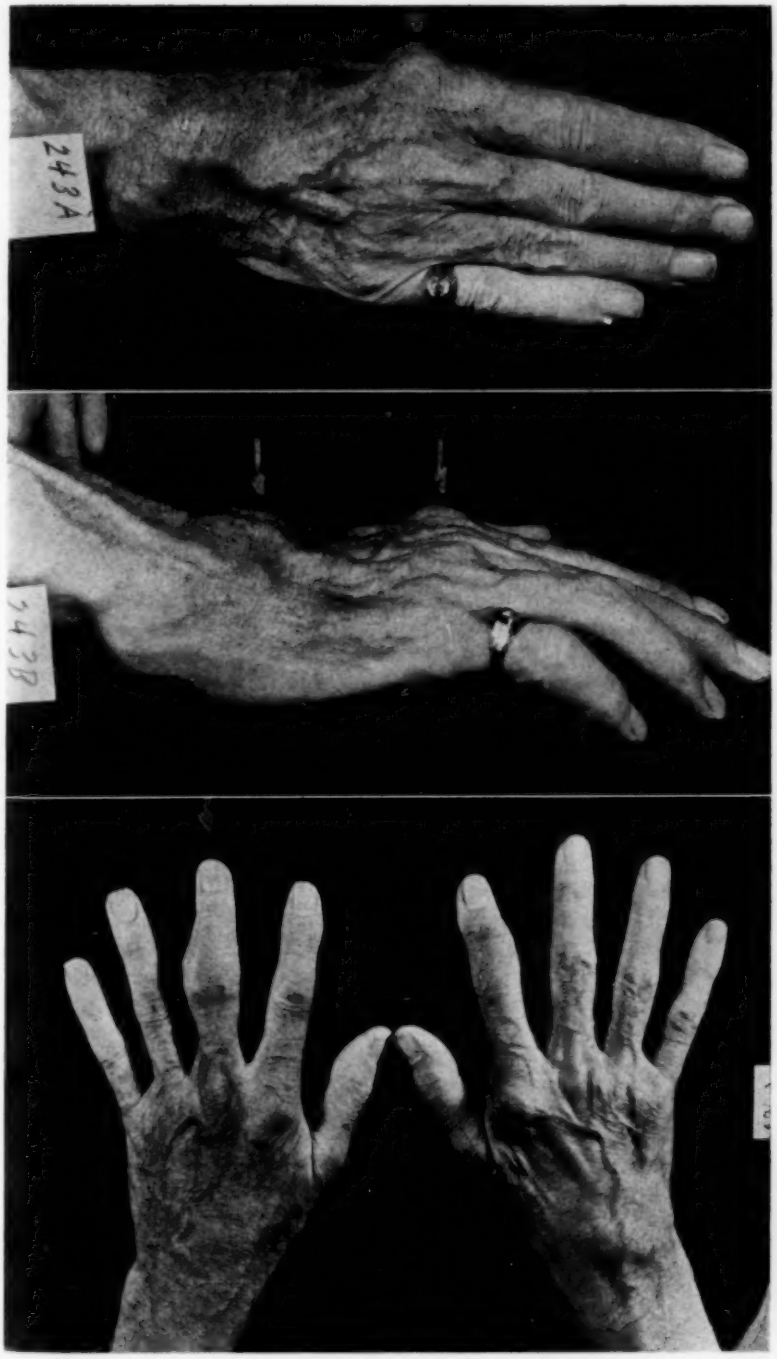

FIG. 1. (*Top*) Right hand. Note prominence at base of index finger. This was very hard. Atrophy of small hand muscles can be seen.

FIG. 2. (*Center*) Prominence at base of right index finger and firm swelling ("ganglion") of dorsum of wrist. At operation, the ganglion was found to contain milky fluid and the surrounding soft tissue contained calcium.

FIG. 3. (*Bottom*) Fusiform left third finger. Compare with figure 4.

left axis deviation; hemoglobin 13.1 gm./100 c.c. blood; red blood cells 4.0 million per cubic mm.; white blood count 6250/cu.mm. with normal differential count; and a negative blood Kahn test. The sedimentation rate was elevated to 48 mm. in 45 minutes (modified Westergren method). Examination of the urine revealed 1 + proteinuria, specific gravity 1.010, and rare granular casts and many white blood cells on the microscopic examination. The phenolsulfonphthalein test yielded 20 per cent excretion in two hours. The non-protein nitrogen was 45 mg. per 100 c.c. of blood and the fasting blood sugar was 80 mg. per 100 c.c. (Studies at another hospital in 1939 had revealed a "normal" non-protein nitrogen and a "normal" phenolsulfonphthalein excretion.) Gastrointestinal roentgen-rays were negative except for "moderate functional stasis." Flat film of the lower abdomen and pelvis revealed "hypertrophic proliferative changes in the region of both femoral greater trochanters." Roentgen-rays of the entire spine revealed advanced osteoarthritic deformities of the last four cervical vertebrae, characterized by anterior and posterior lipping and spurring of the bodies. There was a loss of normal anterior curvature, and a marked left-sided scoliosis of the upper thoracic spine with the apex of maximal convexity at T_8. There was bony atrophy and minimal lipping of the lumbar vertebrae. Chest roentgenogram revealed arteriosclerosis of the aorta with normal sized heart. There was no pulmonary infiltration. The intravenous pyelogram was within normal limits.

The patient was afebrile during his six-week period of observation. His arthritic complaints were helped greatly by physiotherapy. When he was discharged, he returned to the care of his own physician who continued the use of Ertron, 200,000 units per day. After five more months (10 months since the original onset of vitamin D medication) the patient first noted the appearance of subcutaneous nodules, several of which were painful, involving both wrists and forearms. These gradually increased in size, although the patient believed that several actually became smaller. The arthritic pains of the various joints, especially those of both hands and of the cervical spine, varied in intensity. He entered the hospital on July 11, 1946 because of an increase of his arthritic pain and because of the subcutaneous nodules of both arms. Generalized pruritus, mainly of the trunk, was mentioned on admission. Other medications, besides Ertron, taken by this patient, were a preparation containing vitamin B-complex 3 capsules per day; brewers' yeast, 2 gm. per day; "large doses" of thiamin hydrochloride intravenously; sodium salicylate, 1.5 to 2.0 gm. per day; Metamucil for a period of four months; Pavatrin (anti-spasmodic); and Ventriculin (liver-stomach preparation) for anemia daily for a period of three months; and doses of codeine when needed.

Salient features of the physical examination (July 11, 1946) were: Blood pressure, 145 mm. of mercury systolic and 80 mm. diastolic. Head, eyes, ears, nose and throat were within normal limits. The lungs were clear to percussion and auscultation. The heart was slightly enlarged, the left border extending 2 cm. to the left of the mid-clavicular line. The heart sounds were of good quality. There was a short soft systolic apical murmur. The abdomen was negative. There were bilateral indirect, inguinal herniae. The third left finger was greatly swollen (figure 3). There were between 10 and 15 small, scattered, slightly tender subcutaneous nodules, which varied in consistency from "fibrous" to "calcific." There was marked atrophy of the small hand muscles and lesser atrophy of the muscles of the forearm. There was tenderness over the cervical spine and tenderness and warmth of the finger and wrist joints, but little limitation of motion. Neurological examination was unremarkable.

The patient was placed on a low calcium (100 mg. a day) diet, and Ertron was stopped. He was given aspirin (0.6 gm. four times daily) and codein (0.06 gm. doses as required) for his rheumatoid arthritic pains: Ferrous sulfate (0.2 gm. thrice daily) was given for the secondary anemia. Physiotherapy (whirlpool baths, radiant heat to the spine, and paraffin baths to the hands) was instituted.

FIG. 4. (*Above*) Roentgen-rays of left hand. Calcification can be seen in the soft tissues of the left third finger and on the ulnar side of the wrist.

FIG. 5. (*Below*) Roentgen-rays of right hand. Note subcutaneous calcification at dorsal and ulnar portions of the wrist.

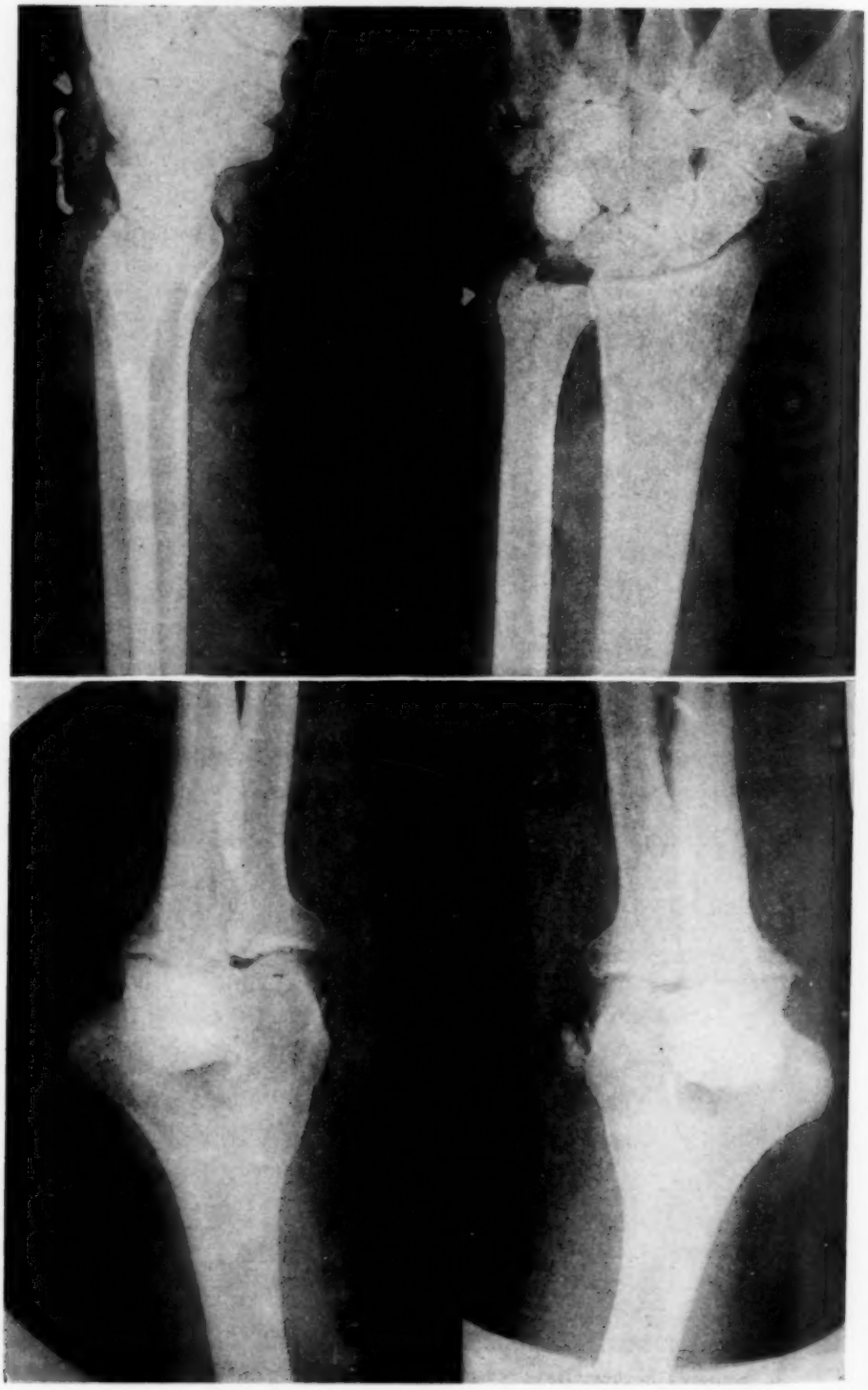

FIG. 6. (*Above*) Roentgen-rays of left hand. Subcutaneous calcification of the wrist.
FIG. 7. (*Below*) Roentgen-rays of left elbow. Arrow indicates calcification.

Electrocardiograms were normal. Gastric analysis revealed 2° free HCl in one specimen (after histamine, 0.5 c.c., hypodermically). Sternal marrow puncture was interpreted as revealing a moderate normochromic anemia, with a slight increase in erythropoiesis and no evidence of aplastic changes. Numerous roentgen-rays revealed advanced osteoarthritic changes in the bodies of the lower cervical spine with narrowing of the intervertebral discs between the C-5 and -6 and C-6 and -7; moderate osteoporosis of the thoracic spine; slight sclerosis of the margin of the left sacroiliac joint. A calcified density (5 by 2 cm.) was shown in the right lung (figure 9b); and calcific deposits about both elbow joints (figure 7), ankle joints, phalangeal joints of fingers and toes, near both ischial tuberosities (figure 8), and in the left axilla. A flat film did not show any intra-abdominal calcification.

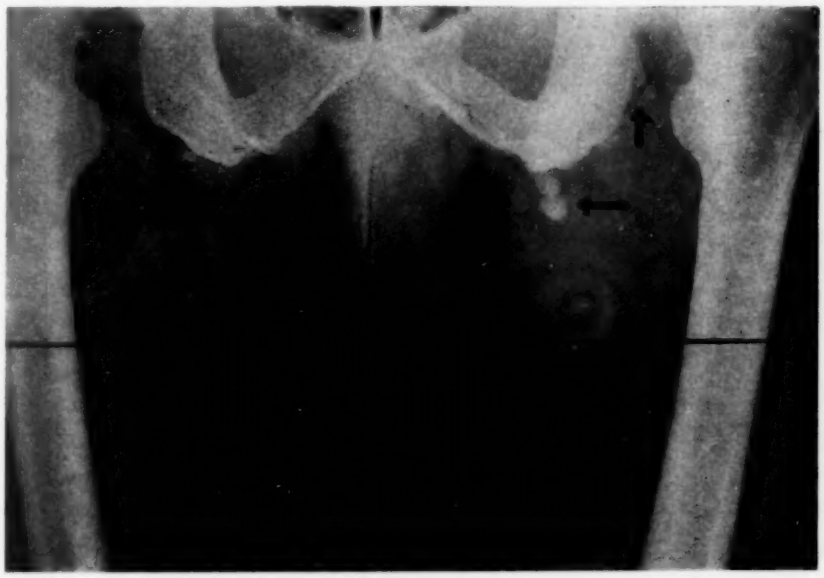

FIG. 8. Roentgen-ray of pelvis. Calcification can be seen.

The laboratory findings are summarized in table 1.

An attempt to biopsy one of the nodules of the right wrist yielded "thick, creamy material," which appeared to be calcific material on smear. Another nodule, which appeared to be a ganglion, was excised from the dorsum of the right wrist. The ganglion was "found to be firmly adherent to the surrounding soft tissue which contained multiple small particles of flaky calcium. The tendon sheaths of the long extensors of the thumb and the index finger were firmly adherent to the ganglion and also contained large quantities of calcium . . . approximately 3 c.c. of milky fluid were obtained from the ganglion" (surgeon's operative note). The ganglion and surrounding soft tissue containing calcium were removed en masse.

The patient's anemia responded well to ferrous sulfate. His rheumatic pains varied with the weather, but usually were not severe. However, codein was required several times weekly for the control of his discomfort and pain. Both the patient and physicians noted the diminution in size of the nodules of the fingers and wrists. Serial roentgen-rays of the hands and wrists revealed a "marked reduction in the periarticular calcification."

TABLE I

Summary of Laboratory Findings

	1939	Aug. 1945	July 1946	Aug. 1946	Sept. 1946
	(Ertron 200,000 units started January 1945)		(Ertron stopped July 11, 1946 after 17 month's therapy)		
		(7 mos. of Vit. D)			
A. Blood					
1. Non-protein nitrogen (mg./100 c.c.)	"normal"	45	85	52	60
2. Urea nitrogen (mg./100 c.c.)			43	26	30
3. Uric acid (mg./100 c.c.)			3.8	3.6	3.3
4. Creatinine (mg./100 c.c.)				2.4	2.1
B. Serum					
1. Calcium (mg./100 c.c.)			9.3–10.2	10.5–10.7	11.4
2. Phosphorus (mg./100 c.c.)			4.5–4.8	3.5–3.6	3.8
3. Alkaline phosphatase (Bodansky units)			6.5	1.6	4.5
4. Albumin (gm./100 c.c.)			3.5	3.9	4.5
5. Globulin (gm./100 c.c.)			3.0	2.3	2.3
6. Icteric index			10	10	11
C. Blood Counts					
1. Hemoglobin (gm./100 c.c.)		13.1	9.1	12.2	12.5
2. RBC (millions/cu.mm.)		4.0	2.8	4.0	4.1
D. Urine					
1. Albumin		1+	1+	Neg.	Neg.
2. Microscopic		Rare gran. casts; pus	Occas. WBC.	Neg.	Neg.
3. Calcium excretion (mg./24 hrs.)			460	520	610
E. Basal Metabolic Rate			−20%	−13%	−11%
F. Phenolsulfonphthalein Test (Two hour excretion in per cent)	"normal"	20%	45%		35%
G. Concentration and Dilution Test (Maximum concentration)				1011	1012
H. Blood Pressure		145/100	145/80	140/82	144/84

COMMENT

Increased use of vitamin D has resulted in the publication of numerous reports of vitamin D intoxication. The rationale for the use of a medication (large doses of vitamin D) of doubtful therapeutic value, at best, and of toxic nature, is not clear.

Metabolic study of a patient [12] has revealed that "large doses of vitamin D (Ertron) reduced the fecal excretion of calcium on the low-calcium diet and increased the fecal loss of calcium while the patient was on a high-calcium diet." Vitamin D in large doses is known to cause decalcification of bone, albuminuria, renal insufficiency, hypercalcemia, and metastatic calcification within various tissues and organs. It is important to note that hypercalcemia is not a prerequisite

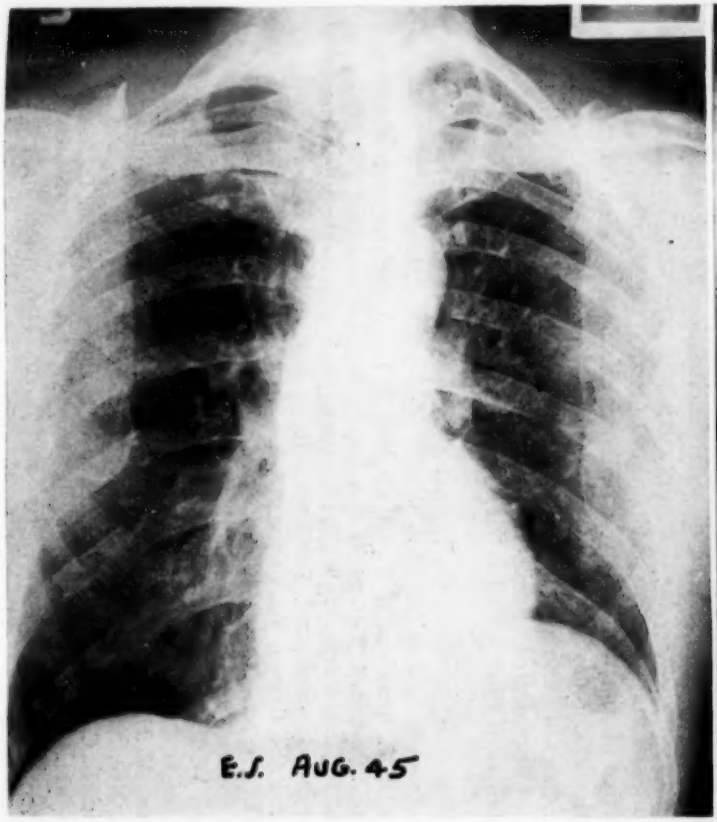

FIG. 9a. Chest film taken in August 1945 was normal.

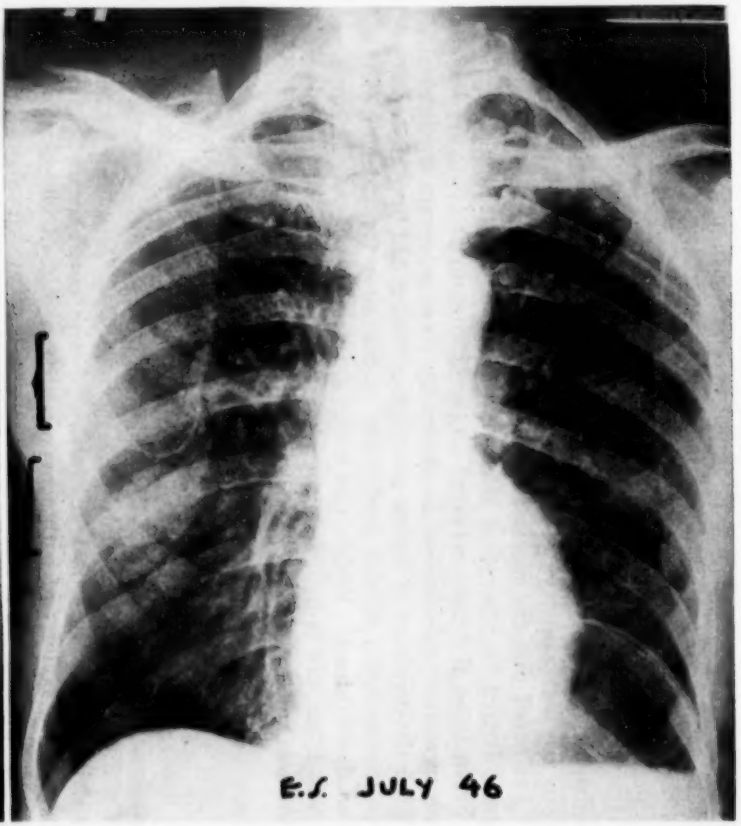

FIG. 9b. In July, 1946, after 17 months of Ertron therapy, calcification can be seen in the right mid-lung field. There are two large areas of calcification. (The upper area is difficult to see in this reproduction.)

to tissue calcification. Freeman et al.[12] emphasize that a high-calcium and phosphorus intake (e.g. 1 qt. of milk daily) increases the toxicity of vitamin D.

Therapy

Immediate cessation of vitamin D therapy and a low-calcium diet plus symptomatic care are the mainstays of treatment of the toxic effects of vitamin D. Ashford [8] has noted that the metastatic calcification produced experimentally in rabbits was followed by resorption after vitamin D administration was discontinued. Freeman et al.[12] have reported a case of vitamin D (Ertron) intoxication whose metastatic calcification as shown by roentgenogram diminished six months "after the ingestion of Ertron and high-milk diet had been discontinued."

The patient reported in this paper was placed on a low-calcium diet, and Ertron was discontinued. Within two months, roentgen-rays of the hands and wrists revealed "marked reduction in the periarticular calcification." Pulmonary calcification was unchanged.

Summary and Conclusions

Large doses of vitamin D taken over a period of time may be toxic and can cause metastatic calcification, renal failure, and death. The case reported here is that of a 59-year old white male who received 200,000 units of vitamin D (Ertron) daily for a period of 17 months, and who noted the development of hard, subcutaneous nodules of both arms after 10 months of vitamin D medication. Roentgenograms revealed extensive subcutaneous calcification throughout the body. Despite the absence of renal calcification by roentgen-ray and the absence of hypercalcemia, renal insufficiency was present. Therapy included a low-calcium diet and cessation of vitamin D (Ertron) medication. This resulted in a reduction of subcutaneous periarticular calcification, as seen on roentgen-ray, and symptomatic improvement.

Large doses of vitamin D are of doubtful value in the treatment of rheumatoid arthritis. Concentrated vitamin D medication may be toxic when used over prolonged periods of time.

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STRUMA LYMPHOMATOSA *

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Hashimoto in 1912 described a clinical and pathological entity which consisted of diffuse enlargement of the thyroid in females with evidence of rich infiltration of the thyroid with connective tissue and lymphocytes and lymphoid hyperplasia. This condition not only has been called Hashimoto's disease but also struma lymphomatosa.

Since 1912 it has been debated as to whether this is a distinct clinical entity or a stage of Riedel's struma, as was suggested by Ewing [1] in 1922. Several excellent reviews in the past few years indicate, however, that there is a distinction between struma lymphomatosa and Riedel's struma. Joll [2] in 1939, McSwain and Moore [3] in 1943, Lee [5] in 1935, Clute [6] et al., and others [4] have supported the idea that struma lymphomatosa is a separate clinical entity. In 1943, McSwain and Moore,[3] in a review of the literature, found only 71 cases

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The Chief Medical Director of the Veterans Administration assumes no responsibility for the opinions expressed or conclusions drawn by the authors.

which were reported in sufficient detail to accept as unquestionable struma lymphomatosa.

Clinical Manifestations. This condition is found usually between the ages of 40 and 50 and occurs almost exclusively in women. Only three cases have been reported in men. There is usually a firm, diffuse enlargement of the thyroid and mild pressure symptoms such as hoarseness, dysphagia, aphonia, tight feeling in the throat, cough, and substernal pressure. The patients may have myxedematous features such as easy fatigue, mental depression, gain in weight, dryness of the skin, lethargy, etc. However, in rare cases, tremor, nervousness, palpitation, anorexia, fatigue, loss of weight, insomnia, irritability and other symptoms suggesting hyperthyroidism may be present. Schilling [6] states that the symptoms that occur suggesting hyperthyroidism are secondary to the pressure locally and its effect on the sympathetic nervous system, rather than true hyperthyroidism. He also states that the complaints of patients with struma lymphomatosa are always vague with the exception of the goiter and a sense of fullness in the throat. Bothe [7] believes that hyperthyroidism may be associated with struma lymphomatosa, and he presents one case with a basal metabolic rate of plus forty-six. It seems to be agreed, however, that eventually in all cases, hypothyroidism makes its appearance and myxedematous features later appear.

Etiology. This condition is a clinico-pathological entity of unknown etiology. Many things have been suggested such as vitamin deficiency,[9] overstimulation of the thyroid by the pituitary thyrotrophic hormone,[10] and, as suggested by Schilling,[6] the possibility of this condition being a degenerative process, in contrast to a neoplastic or inflammatory process. By degeneration it is believed that through the years the gland burns itself out due to the demands of the body. The lymphoid infiltration and hyperplasia that occur are a compensatory and replacement process for the slowly degenerating acini.

Laboratory Findings. The laboratory offers very little aid in the diagnosis. The basal metabolic rate may be high or it may be low. Usually it is low and, as the disease progresses, the basal metabolic rate tends to become lower. McSwain [3] mentions also that a relative lymphocytosis may exist.

Pathology. In struma lymphomatosa, according to Schilling,[6] the thyroid is diffusely enlarged and may proceed posteriorly and encircle the trachea. The surface of the gland is smooth, pinkish in color, and has a pseudo-lobular appearance. The cut surface appears to be finely lobular with a yellowish cast which is characteristic. There is a diffuse and uniform degeneration of the acini. The epithelium is flattened with eccentrically-placed dark nuclei. The acini shrink, and pale, degenerate cells are seen. The colloid is scant. There are numerous lymph follicles. Plasma cells are occasionally seen. No undue vascularity is noted. There is diffuse infiltration of lymphocytes throughout the gland, in the cells, and between the acini. There is an increase in fibrous connective tissue surrounding the lobules of degenerating acini. This fibrosis increases as the disease progresses. Late in the disease, there may be a complete fibrous replacement of the lobule of the thyroid. This fibrosis is, however, a fine waving type and assumes characteristic waving whorls about the lobules.

Treatment. Struma lymphomatosa responds readily to roentgen therapy.[6] A positive diagnosis is essential, and, when the diagnosis is in doubt, a biopsy of the thyroid should be taken before surgery. This is recommended because the progress of the disease is usually toward myxedema, and surgical removal of the

thyroid tissue will only precipitate this condition. If the obstructive symptoms are too marked, or if hyperthyroidism exists,[11] then surgery may have to be done. Following roentgen-ray therapy, the response is rapid and the gland will shrink markedly in size in two or three weeks.

The following is a case report of a patient with struma lymphomatosa. This case presented several interesting features.

Case Report

H. F. H., white male, aged 48, occupation clerk, was admitted to the hospital on April 5, 1945. The patient's past history was negative, except for a hemorrhoidectomy

Fig. 1. Section of thyroid showing typical lymphoid hyperplasia with follicle formation.

in 1917, and a herniorrhaphy in 1938. His general health had always been excellent. The onset of the present illness was in February, 1945, when he suddenly became acutely ill with fever and multiple joint pains. The joints were described as being tender, painful, swollen, and with marked limitation of motion. The elbows, knees, and ankles were the chief joints involved. At this time, he was hospitalized in a private hospital where he remained for about one month. He, apparently, became symptom free and was discharged only to have a recurrence of these symptoms in a few days. It was at this time that he came under our observation. In addition to the joint symptoms, the patient complained of nervousness, choking sensation, difficulty in swallowing, loss of 10 to 15 pounds of weight, restlessness, irritability, free perspiration, and a low grade fever. He stated that he preferred cold weather to hot weather. His appetite had been good and no diarrhea had been noted. The remainder of the history was not contributory.

On physical examination, the patient was found to be well developed and he did not appear acutely ill. He was quite nervous, and during the initial interview he constantly twisted and turned in his chair, and would wring his hands frequently. There was advanced pyorrhea of the gums. There was no exophthalmus, lid lag, stare, or lack of convergence of the eyes. A definite fine tremor of the eyelids, tongue, and outstretched fingers was observed. The thyroid gland was enlarged and this appeared to be more noticeable on the right side of the neck. The thyroid was firm and appeared diffusely enlarged and the trachea was not deviated. The blood pressure was 110 mm. Hg systolic and 80 mm. diastolic and the pulse rate was 96. The heart was

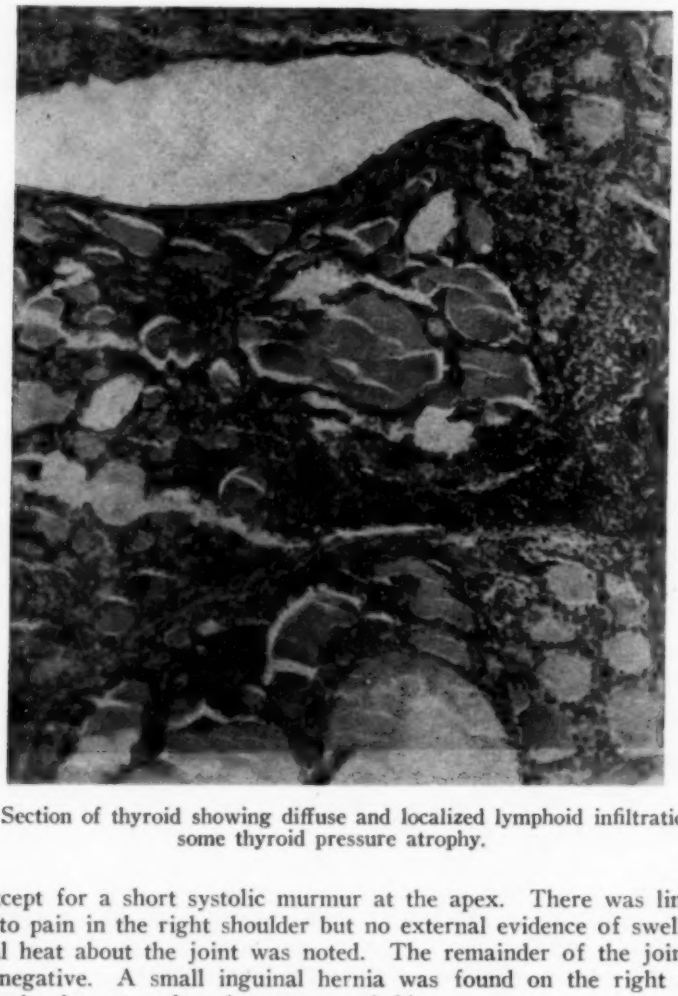

FIG. 2. Section of thyroid showing diffuse and localized lymphoid infiltration with some thyroid pressure atrophy.

negative, except for a short systolic murmur at the apex. There was limitation of motion due to pain in the right shoulder but no external evidence of swelling or increased local heat about the joint was noted. The remainder of the joints, at this time, were negative. A small inguinal hernia was found on the right side. The physical examination was otherwise not remarkable.

The laboratory studies showed the urine to be negative. A smear for malaria was negative. The red blood count was 4,350,000 with a hemoglobin of 16 grams. The white blood count was 8400 with 64 per cent polymorphonuclear cells, 23 per cent lymphocytes, and 3 per cent monocytes. The Kahn, Kline, and Wassermann tests were negative. The sedimentation rate was 20 mm. in one hour. A throat culture

was negative. Roentgen-rays of the elbows, left knee, and left ankle were negative. The roentgen-ray of the heart and lungs was negative. The electrocardiogram showed sinus tachycardia but was otherwise negative. Agglutination for undulant fever, typhoid, paratyphoid A and B, and proteus X–19 were all negative. Basal metabolism tests were attempted on several occasions, but the patient would become apprehensive and complain of choking and smothering each time the test was attempted. Blood cultures were negative.

At the time of admission the patient was placed on bed rest, salicylates, multiple vitamins, a high caloric and a high vitamin diet. He continued to have acute involvement of various joints with redness, swelling, increased heat and pain all being present, in addition to a low grade fever. He was tried on a therapeutic course of sulfadiazine, but he received no appreciable benefit. Due to the pyorrhea of the gums, and evidence of oral caries, his remaining teeth were extracted in an attempt to clear up this possible focus of infection. In spite of the above therapeutic approach, the patient continued to run a low grade fever, lose weight, complain of weakness, nervousness, palpitation, choking sensations in the throat and smothering spells. His pulse was consistently elevated, with a rate as rapid as 140 at times recorded. Attempts were again made to get a basal metabolism test, and, finally, a recording of plus 69 was obtained. It was not believed to be a satisfactory test due to the inability of the patient to coöperate. The joint symptoms had subsided, and after observation by both the medical and surgical services, it was decided to place the patient on Lugol's solution and, if he responded clinically, surgical removal of the thyroid would follow. After Lugol's solution was administered, it was noted that the patient was improved and on August 13, 1945, a subtotal thyroidectomy was performed. The thyroid was two and one-half times normal size at operation. It was dense, firm, and hyperplastic in appearance. A few nodulations were noted in the right lobe, but the thyroid appeared to be diffusely involved. The pathologic report is as follows:

Gross: Specimen consists of two lobes of thyroid tissue, one measuring 6 by 5 by 3½ cm., the other 7 by 5½ by 4 cm. in diameter. Both lobes are surrounded by well formed capsules. The surface is irregularly nodular and moderately firm in consistency. The cut surface of the thyroid is dullish gray in color with scattered, grayish-white, small nodules varying up to 1 mm. in diameter. In a few areas there is suggestive increase in the connective tissue. Histological examination of sections of the thyroid tissue shows areas of normal thyroid acini completely filled with collagenous colloid. The lining epithelium is low cuboidal. There is no evidence of hyperactivity of the gland. In many areas there is a diffuse, lymphocytic infiltration crowding out the thyroid tissue. In other areas there is definite lymph follicle formation with large germinal centers. In these areas there is pressure atrophy of the surrounding thyroid tissue. Scattered through these areas are also some slight increases in the interstitial connective tissue. In view of the diffuse overgrowth of lymphoid tissue and the formation of lymph follicles containing large germinal centers, as well as the slight increase in the connective tissue, it appears that we are dealing with a struma lymphomatosa.

In view of the fact that this is a rare disease, the microscopic sections were referred to N. Chandler Foot [12] for review. He stated that they were in every way typical of struma lymphomatosa. He also stated he had seen only two previous cases in male patients.

The postoperative course was complicated by an acute exacerbation of the joint symptoms with the right hand, right wrist, right elbow, and right knee being swollen, red, and painful. There was an accompanying rise in temperature to 102°. He developed a cough and expectorated mucopurulent material. A roentgen-ray of the chest on the second postoperative day showed an area of

cloudiness in the midportion of the right lung along the periphery. The patient was placed on penicillin and his fever and clinical symptoms slowly abated. He became symptom free, began to gain weight, and reached a peak of 167 pounds before his discharge. His weight had dropped to 146 pounds prior to surgery. His nervousness decreased and he improved. He was discharged on October 11, 1945.

Since discharge it is reported that this patient is working daily and at present has no symptoms indicative of hypothyroidism or of myxedema.

Summary

1. A review of the clinical manifestations, etiology, laboratory findings, pathology, and treatment of struma lymphomatosa is presented.

2. A case report of struma lymphomatosa occurring in a white male, with clinical evidence of hyperthyroidism, is also presented. The occurrence of this condition in males is very rare. The presence of symptoms suggesting hyperthyroidism, as noted in this patient, is not the usual clinical picture.

3. The difficulty in establishing the diagnosis without microscopic sections of the thyroid is clearly demonstrated in this case.

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PRIMARY LYMPHOSARCOMA OF THE LUNG (A CASE REPORT AND REVIEW OF THE LITERATURE) *

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The medical literature contains many references to sarcoma of the lung. These may originate in connective tissue or lymphoid tissue. However, previ-

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ously reported tumors have always shown involvement of other structures than lung, usually the mediastinal lymph nodes. Thus, it has been difficult to say where the tumor arose. Falconer and Leonard [1] reported a series of 25 cases of lymphosarcoma of the lung and mediastinum. None of these involved the lung alone. Cutler [2] reported a series of 30 cases of lymphosarcoma, one of which was lymphosarcoma of the lung. However, no microscopic description was given and there was no indication of its being limited to, or primary in, the

FIG. 1. Photograph of lower lobe of right lung showing the tumor mass cut across.

lung. O'Donnell [3] reported two cases of lymphosarcoma of the lung. Both of these showed involvement of tissue other than lung and may well have originated in the mediastinum. Peters [4] reported 13 cases of sarcoma of the lung and mediastinum; no microscopic description was included in the report.

A case of lymphosarcoma was described by Pekelis.[5] Microscopic description revealed it as a "small cell" lymphosarcoma arising from the peribronchial lymphoid tissue of the lung. Grossly, the tumor was a large mass the size of a small orange infiltrating the lower lobe of the left lung. It was hard and nodular and yellow-pink in color. There were metastases in the sternum, in the fourth and fifth right ribs and in the liver. The mediastinum and other thoracic structures were not involved.

The case presented herewith is one in which the lesion is limited to the lower lobe of one lung. There is no doubt of its origin in the lung, since no other structures in the body are involved. The case reported by Pekelis [5] is the one other case in the literature in which the sarcoma can definitely be said to originate in the lung.

Case Report

The patient, a 34 year old white female, was admitted October 7, 1944 to the Jewish Hospital of Brooklyn on the service of Dr. Rudolph Nissen with a history of

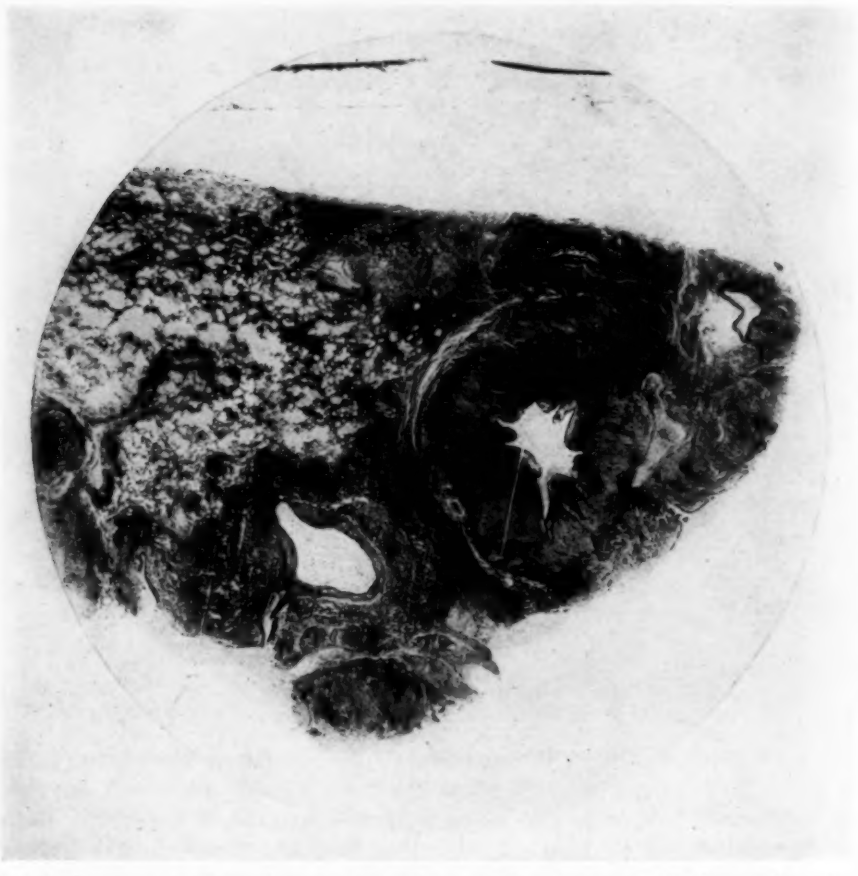

Fig. 2. Low power photomicrograph showing a collar of tumor cells about a bronchus. H & E. ×10.

hemoptysis for three months and occasional right chest pain for the same period of time. The family history was negative.

In July 1944, patient noted blood streaked sputum. She had no real chest pain but felt some slight discomfort in the chest. She had a moderate cough for three months preceding admission. Roentgen-ray before admission revealed a small egg-shaped mass in the right chest.

On physical examination there was an area of slight dullness below the angle of the right scapula and in the right base with occasional rhonchi and medium moist râles. Sedimentation rate was 77 mm. per hr.; otherwise the laboratory findings were not remarkable. Bronchoscopy on October 11, 1944 revealed evidences of suppuration in the lower lobe of the right lung. Roentgen-ray, October 16, 1944, revealed an area of homogeneous opacity in the lower right pulmonic field peripherally, which was suggestive of encapsulated fluid. In lateral view, the lesion was confined to the right lower lobe posteriorly. In this view, the lesion had a mottled appearance.

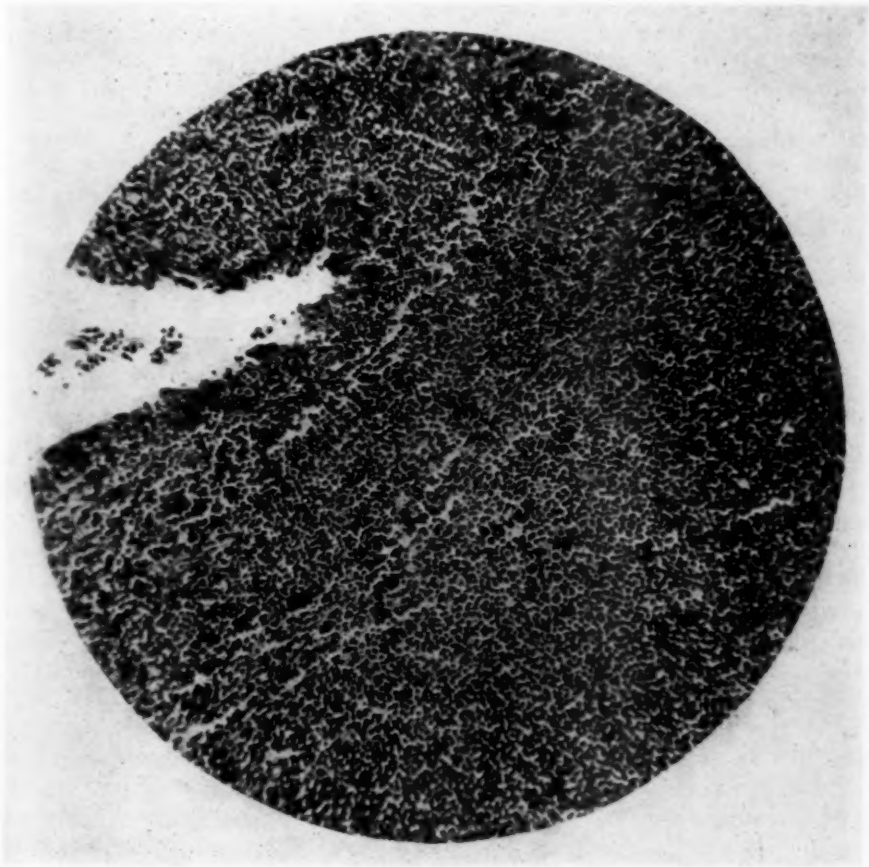

FIG. 3. Low power photomicrograph showing general cytoarchitecture of the tumor infiltrating wall of a bronchus at lower edge. H & E. × 100.

On October 20, 1944, the patient was discharged with a diagnosis of lung abscess to be treated with penicillin at home. The patient was again admitted to the hospital January 21, 1945 (three months later). Her condition had remained about the same during the interval and she had gained 10 lbs. At this admission she complained of cough, bloody sputum and occasional gnawing pain in the right anterior chest.

On physical examination her blood pressure was 128 mm. Hg systolic and 82 mm. diastolic, the breath sounds were increased throughout posteriorly and there were occasional evanescent fine râles at the angle of the right scapula.

Roentgen-ray of the chest on January 22, 1945 showed an area of opacity at the right base posteriorly. On lateral view, it was not homogeneous. There was an area of infiltration within which there may have been necrotization, but a definite fluid level was not demonstrated. On the lateral view, there were two nodular opacities, one just below the root and the other slightly anterior to the infiltrated area.

The patient was operated on January 26, 1945 and the lower lobe of the right lung was removed.

The post-operative roentgen-rays on nine occasions revealed a hydropneumothorax with slowly expanding upper and middle lobes of the right lung.

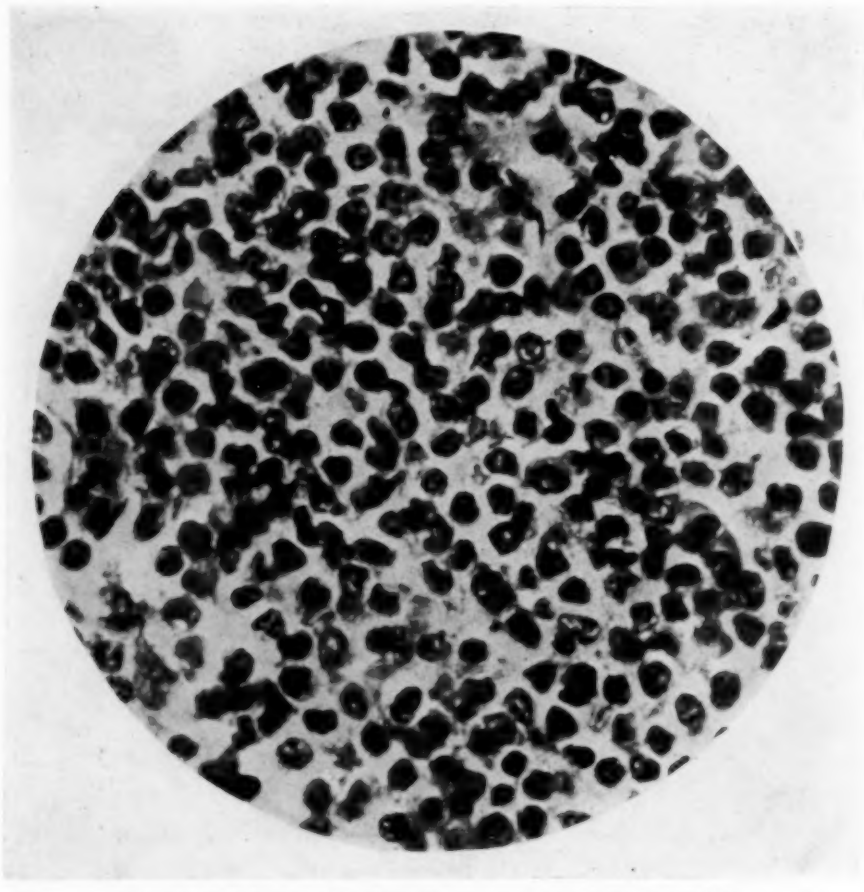

FIG. 4. High magnification of tumor cells. H & E. × 400.

Urine and blood examinations were not significant. Sedimentation rate was 83 mm. per hr. On March 25, 1945, the patient was discharged with the diagnosis of lymphoblastoma (lymphosarcoma) of the lung and empyema thoracis, post-operative.

PATHOLOGY

Gross Description: The specimen consisted of the lower lobe of the right lung. It measured 17 by 11 by 3.5 cm. The external surface was purple red and gray pink

with a reticular gray white pattern. It was smooth and glistening except in several small areas where it was roughened by fibrous tissue tags. In the central portion an irregular egg-shaped moderately firm mass was palpated and the surrounding lung tissue was subcrepitant. On cut section, a good portion of lung tissue was replaced by moderately firm gray white, pink gray, and gray yellow tissue. It occupied an irregular area measuring 7 cm. in greatest diameter. The borders faded imperceptibly into the surrounding lung tissue. A bronchus measuring 0.9 cm. in diameter extended into the mass and fused with it. The lung tissue was pink gray and in places there were small bronchiectatic cavities.

Microscopic Description: The striking picture in preparations from various portions of the lung through the tumor mass was the collar of cells about bronchi and bronchioles and to a lesser degree about the blood vessels. In many of the bronchioles the lining cells were partly or completely desquamated, and some contained a purulent exudate. The tumor cells were of large round cell variety. Many were lymphoblasts and a few showed mitotic figures. In all the preparations, the cells about the lining bronchial epithelium merged with the sheets of cells forming the collar about them. These tumor cells were also seen in places extending along the septa to the deeper portions. The alveolar spaces in places contained foam cells and mononuclear cells with pigment granules, as well as polymorphonuclear leukocytes. The cartilage plates about the larger bronchi appeared compressed. Some areas showed atelectasis while others showed compensatory emphysema. Foci of extravasated blood were also present.

Diagnosis: Lower lobe of right lung with lymphoblastoma (lymphosarcoma).

Discussion

Lymphosarcoma, primary in the lung, is a rare lesion. Lymphoid tissue, from which lymphosarcoma arises, is widely distributed throughout the body and is particularly abundant in the mediastinum. Most of the reported cases of lymphosarcoma of the lung involved mediastinal or other thoracic tissues. It is very likely that these reported tumors arose in lymphoid tissue outside the lung and only secondarily involved the lung. Only one case was seen in the literature where it can definitely be said that the lymphosarcoma originated in the lung. The case reported above is one of the rare cases in which the lesion is so situated anatomically, that at operation or autopsy, it can be said definitely to have arisen in the lung. Obviously, the case must have been seen early in its course since it involved only one lobe of the lung and no other tissue. Peters [4] concluded, after reporting 13 cases of lymphosarcoma of the lung and mediastinum, that it is difficult to say which is involved first, the lung or mediastinum, unless the case is seen early. He further concluded that the mediastinum is more often the original seat of the growth.

As a further indication that only the lung was involved, the patient is alive and well 14 months after operation, with no evidence of metastasis or extention at this time.

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CERVICAL ACTINOMYCOSIS WITH EMBEDDED FOREIGN BODY AND WITHOUT SINUS FORMATION *

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and WILLIAM C. HUMPHRIES, Capt., M.C.,
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CERVICOFACIAL actinomycosis is the most common type of this disease and the type which is most readily amenable to combined medical and surgical treatment. No attempt is made to review the literature; this case is presented because it is interesting, and unusual in that an embedded foreign body was present and no sinus formation developed.

CASE REPORT

A 30 year old private was admitted to Army Hospital on November 8, 1945 complaining of painless swelling of the glands in the left side of his neck.

Family History: Non-contributory.

Past History: Patient was born and reared in East Orange, N. J., and lived there all his life before entering the army. He had the usual childhood diseases and scarlet fever without sequelae. He had always enjoyed excellent health. He had been married for 10 years and had five children.

Present Illness: While on maneuvers in early August 1945, near Camp Claiborne, La., he dived into a pile of hay and a long piece of straw entered his mouth. He immediately pulled the straw out, but felt that a small piece had remained embedded under his tongue on the left side. The straw abraided his throat but this healed after four or five days. He reported to the doctor immediately after the accident and no foreign body was found in his mouth. Ten days after the injury he first noticed swelling in the left side of his neck. This was painless and not red and he had no constitutional symptoms. The swelling gradually increased and on November 8 he was admitted to the Regional Hospital at Ft. Jackson, S. C. He was under observation in this hospital for seven weeks, and during this period of time the swelling in the left side of the neck gradually increased. Late in November 1945 he again had the sensation that some foreign body was present in the left side of his neck but no lesion of the mucous membrane was found.

Early in December the skin over the swelling on the left side of the neck became red and he was treated with penicillin from December 10 to 13 receiving 30,000 units every three hours. The swelling decreased somewhat and the redness subsided. He was transferred to Oliver General Hospital on December 17, 1945.

Physical examination on December 18 showed temperature 97.8°, pulse 74, respirations 16, weight 172 lbs. and blood pressure 115 mm. Hg systolic and 70 diastolic. Patient was a well developed, well nourished, healthy looking man. There was a hard brawny mass in the left submandibular area extending down to the supraclavicular region. The overlying skin was red and attached to the underlying tissue. There

* Received for publication July 2, 1946.

was no definite fluctuation and no lymph nodes could be definitely and distinctly palpated. Trachea was displaced slightly to the right. Head, eyes, ears, and nose were normal. Direct laryngoscopy showed nothing abnormal. Lungs were clear. Heart was normal. Abdomen, genito-urinary tract, and glandular systems were negative. Muscular system was well developed. Neurological examination was normal. There was no abnormality of the bones or joints.

Laboratory studies showed hemoglobin 94 per cent; red blood cell count 4.58 million; white blood cell count 7,000 with 65 per cent neutrophiles, 26 per cent lymphocytes, 6 per cent monocytes, and 3 per cent eosinophiles. The sedimentation rate was 28 mm. per hour (Wintrobe). Kahn test was negative. Urinalysis was normal. Tuberculin test was positive with second strength P.P.D. A roentgenogram of the chest was negative. Roentgen-rays of the soft tissue of the neck showed no foreign body and no calcification.

On December 18, 1945, patient was started on sulfadiazine 4 grams daily, penicillin 40,000 units every three hours, and saturated solution of potassium iodide 0.5 gram three times a day after meals, and this treatment was continued until operation on January 10, 1946. During this time he had no untoward symptoms from the drug therapy and the swelling in the left side of the neck definitely decreased. There was much less induration and now numerous hard lymph nodes were palpable. He was then seen by the surgical consultant who felt that operation was indicated. He had no fever except for a slight elevation from January 3 to 5 when he had an acute upper respiratory infection. He still had no constitutional symptoms. Sulfadiazine levels in the blood ranged from 6.6 to 14.3 mg. per cent.

Operation: On January 10, 1946 under a gas-oxygen-ether anesthesia, the mass on the left side of the neck was excised. Enlarged matted glands were found just lateral to the thyroid notch both superficial and deep to the leading margin of the sternocleidomastoid muscle. The glands were removed in two sections; considerable difficulty was encountered because the glands were densely adherent to the adjacent muscle. At the innermost and deepest part of the operative field, a piece of straw 1 cm. in length was encountered and removed. This straw appeared to be coming directly from the tonsillar region. The bleeding points were tied and a rubber tissue drain was inserted in the wound. The subcutaneous tissues were closed with interrupted sutures of No. 80 cotton. The skin was closed with black silk and the patient was returned to the ward in good condition.

Penicillin 40,000 units every three hours was continued after operation until January 16, 1946. Sutures and rubber drain were removed from the incision on January 17 and the wound healed by first intention. Patient was then put on sulfadiazine and potassium iodide in the same dosage as before and this was continued until March 10, 1946. The induration in the neck gradually subsided and the patient remained asymptomatic and afebrile. Pathological examination of the tissue removed at operation showed numerous actinomyces granules with characteristic marginal clubs, surrounded by numerous neutrophiles, mononuclears, and fibrous tissue.

After several weeks' post-operative stay in the hospital, the patient was sent on a 30 day convalescent furlough. When he returned his neck was soft and pliable, there was no redness, and no palpable glands. Apart from the scar, which was placed in a fold and was therefore relatively unnoticeable, the neck appeared to be normal. He gained weight and the sedimentation rate was 12 on March 21, 1946. By private correspondence, the patient reported himself completely well five months after operation.

Summary: A 30 year old man who developed cervical actinomycosis 10 days after injuring the mucous membrane of his oro-pharynx with a straw was treated with penicillin, sulfadiazine, potassium iodide, and surgical excision four

months after onset. There was no sinus formation; a straw 1 cm. in length was found embedded in the diseased tissue. The patient is apparently cured five months after operation.

Discussion

This patient gave a definite history of a foreign body (straw) entering and embedding itself in his oro-pharynx, and he was not sure that all of the straw had been recovered and removed. Several times during the course of his illness, he felt as if there was "something sticking" in the left side of his neck. No one felt that this sensation was due to a foreign body before the straw was found at operation.

After operation, the sensation did not recur and in retrospect, it seems probable that the foreign body had caused the feeling of "something sticking" in his neck. The straw apparently had entered the soft tissues of the neck through the tonsil, since it was found embedded in the tonsillar area during the excision of the diseased tissue.

The fact that no sinus formation developed is very unusual in actinomycosis. The presence of this fungus infection was at once considered likely after a complete history was obtained. Although actinomycosis could not be proved before operation, treatment with penicillin, sulfadiazine, and potassium iodide was started at once. This massive chemotherapy may well have aborted the formation of skin sinuses. Before chemotherapy was started, the involved area was comparatively soft but not fluctuant, and there were no breaks in the skin. During chemotherapy, the soft area gradually decreased in size and became very firm.

After three weeks of medical treatment, it seemed obvious that further change in the involved tissue could not be expected. Surgical treatment was considered necessary and the eventual course of the patient vindicated this decision.

Summary

1. Actinomycosis may be present without sinus formation and with an embedded foreign body.

2. The importance of combined medical and surgical treatment is stressed.

EDITORIAL

THE THERAPEUTIC USE OF NITROGEN MUSTARDS

THE sulfur and nitrogen mustards, because of their use as warfare agents, have been subjected to intensive study, both as to their chemical nature and their action on the tissues. Although originally employed primarily because of their local irritant and vesicant action on the skin and mucous membranes, it was soon recognized that when absorbed they exert a toxic action on a variety of tissues.

In animals subjected to toxic doses,[1] the tissues most severely involved are the mucosa of the gastrointestinal tract and the hemopoietic tissues. There is vacuolization and swelling of the nuclei of the gastrointestinal epithelium, followed by necrosis and desquamation. This is accompanied by severe nausea, vomiting and diarrhea. There is loss of body fluid and electrolytes, which leads to shock and circulatory collapse which is quickly fatal in severe cases. There is also disintegration and destruction of the lymphoid tissues throughout the body and of the hemopoietic cells in the bone marrow, which in less rapidly fatal cases leads to almost complete aplasia of these tissues.

It has been shown that when administered in sublethal threshold doses, the action of these mustards is largely confined to those tissues which normally proliferate rapidly. The first objective evidence of injury is an inhibition of mitotic activity and cellular multiplication. This may occur without other evidence of injury to either the nucleus or cystoplasm of the cell. Experiments with *Tradescantia* pollen and with fruit flies (*Drosophila*) have shown that exposure to mild concentrations of the mustards may cause translocations and other abnormalities of the chromosomes which may be transmitted through successive generations, like those induced by radiation.

Although the toxic action of these substances appears to affect the nucleus primarily, in special instances evidence of probably independent injury to the cytoplasm has been obtained.

The mechanism of the toxic action of the mustards has not been entirely elucidated. The activity of these compounds is attributed to a chemical change which takes place when they are put in aqueous solution, an intramolecular cyclization with formation of a highly reactive onium cation and liberation of Cl-.[1] It has been suggested that cell injury is brought about by interference with the enzyme systems of the cells. There is experimental evidence that the mustards do powerfully inhibit the activity of certain enzymes, particularly the phosphokinases, although many other systems are little affected. Mitosis may be inhibited, however, by concentrations of

[1] GILMAN, A., and PHILLIPS, F. S.: The biological actions and therapeutic applications of the B-chloroethyl amines and sulfides, Science, 1946, ciii, 409–415.

mustards which are below those which are required to affect tissue respiration or glycolysis under experimental conditions.

The capacity of the mustards to inhibit mitotic cell division and their relatively selective action on hemopoietic tissue naturally suggested that they might have therapeutic value in neoplastic diseases, particularly in lymphomata and in the leukemias. Preliminary experiments with animals gave sufficiently promising results to warrant a trial in man. The use of these drugs clinically in this country has thus far been restricted to several qualified institutions to which the material has been supplied by the Committee on Growth of the National Research Council.

The sulfur mustards have been regarded as too highly reactive and toxic for therapeutic use, and the experiments thus far reported have been restricted to the use of two nitrogen mustards, *tris*(beta-chloroethyl) amine hydrochloride and methyl *bis*(beta-chloroethyl) amine hydrochloride. The latter compound has been more extensively used since it appears to be significantly less toxic than the former and equally effective.

These drugs are readily soluble in physiological salt solution. They are intensely irritating to the tissues and must be given intravenously and without leakage. To lessen the tendency to thrombosis it is customary to start an intravenous infusion of saline or glucose solution, and when this is flowing in rapidly to introduce a measured quantity of the drug into the system by piercing the rubber tubing with a hypodermic needle and rapidly injecting the solution. As the drugs speedily undergo chemical change in solution and presumably their effectiveness may thereby be altered, they must be administered immediately (within five minutes) after the solution is prepared. The customary single dose is 0.1 mg. per kilogram of body weight (maximum 8 mg.), and this dose is usually administered on four consecutive days (occasionally six or seven doses have been given). In case of relapse subsequent courses of two to four doses have been given, usually only after an interval of six to eight weeks. The administration of doses twice this size to a few patients has resulted in excessive and alarming depletion of the marrow, although recovery has been almost invariable.

Thus far reports of treatment of about 150 patients have been published (Goodman et al.,[2] 67 cases; Jacobson et al.,[3] 59 cases; ApThomas and Cullumbine,[4] 25 cases). A preliminary summary of the results obtained in the earlier cases treated in this country was published by Rhoads.[5] Although this number is relatively small, it permits some tentative conclusions as to the probable effectiveness and limitations of these drugs.

[2] Goodman, L. S., et al.: Nitrogen mustard therapy, Jr. Am. Med. Assoc., 1946, cxxxii, 126–132.

[3] Jacobson, L. O., et al.: Nitrogen mustard therapy, Jr. Am. Med. Assoc., 1946, cxxxii, 263–271.

[4] ApThomas, M. I. R., and Cullumbine, H.: Nitrogen mustards in Hodgkin's disease, Lancet, 1947, i, 899–901.

[5] Rhoads, C. P.: Nitrogen mustards in the treatment of neoplastic disease, Jr. Am. Med. Assoc., 1946, cxxxi, 656–658.

In nearly all cases nausea and vomiting follow the injections within two to four hours and last for several hours, rarely for 24 to 48 hours. Exceptionally there may be diarrhea and a more protracted anorexia.

Effective doses almost invariably cause some depletion of the hemopoietic tissues. This is the limiting factor in determining dosage. The margin between an effective dose and a seriously toxic dose is narrow. This injury may be evident within 24 hours as shown by a fall in the total leukocyte count and by the presence in blood films of cells showing morphological evidence of degenerative changes, particularly in the nuclei. Both lymphocytes and neutrophilic granulocytes are severely affected; observations as to which are first affected are conflicting, and this probably varies in different cases. There is usually a progressive leukopenia reaching a minimum count of 1000 to 5000 after two to three weeks. There is then a recovery to normal figures within about two weeks, associated with a shift to the left in the granular leukocytes and often the appearance of some myelocytes in the circulating blood. In a few cases, particularly after excessive doses, there has been an extreme reduction, even to 200 per cu. mm. The cases reported in this country have shown no clinical manifestations of agranulocytosis except fever. ApThomas and Cullumbine,[4] however, reported three cases of extreme depletion of all types of marrow cells following administration of the *tris* compound, in which stomatitis appeared. Presumably the administration of penicillin would reduce the risk of such infections.

The platelets are also reduced, usually to from 60,000 to 100,000 per cu. mm. In severe reactions they may be much more reduced, to 20,000 or less, and there may be a prolonged bleeding time, purpura and bleeding from the mucous membranes. There is a gradual recovery which about parallels that of the leukocytes. The red blood cells and hemoglobin as a rule are only slightly reduced (about 300,000 red cells and 1.0 gm. hemoglobin [3]), and there is a marked transient reduction in reticulocytes. ApThomas and Cullumbine,[4] however, observed one patient in whom the hemoglobin fell to 30 per cent. Recovery from such severe reactions is protracted, but no evidence of cumulative injury has been reported.

The most satisfactory clinical results have been obtained in Hodgkin's disease, of which 75 cases have been reported. Many of these were in an advanced stage of the disease and had become resistant to irradiation treatment. The number of early cases, previously untreated, was small. In most of the cases, nevertheless, there was at least temporary clinical improvement of significant degree, and this was not infrequently "dramatic," even in patients who were regarded as resistant to irradiation. In a few cases (3 of 27 cases of Jacobson et al.[3]), however, either no appreciable improvement was obtained or (in five others) it was quite transient. As a rule no basis for predicting an unfavorable result was evident.

In patients responding favorably there was prompt subjective improvement (in one to three days), with subsidence of fever and malaise, return

of appetite and increase in weight and strength. This was observed even in patients who appeared almost moribund. Some patients were able to return to work. Bone pain and particularly pruritus were less regularly relieved. With this subjective improvement there was rapid diminution in size (or disappearance) of the tumor masses and of the liver and spleen.

The remissions so obtained have been brief in most cases, on the average two to three months, exceptionally up to seven months. Relapses usually responded to a second course of treatment, and several patients have been maintained in good health for two to three years by repeated courses of treatment at intervals of two months or more as indicated by their clinical status. In three cases [2] sensitivity to irradiation was thought to have been restored by nitrogen mustard, and one patient obtained a remission after combined treatment although resistant to each procedure when used alone. In other cases the response to treatment was less satisfactory, remissions became shorter, and the patients eventually died of the disease. There is no evidence that any patient has been cured.

In lymphosarcoma the results reported were similar but less regularly obtained and not so well maintained. Of 21 cases reported, some improvement was observed in 13. Excellent results were obtained in some patients, even after they had become resistant to radiation,[2] and in several this was maintained for two years or more by repeated courses.[2]

In 12 cases of chronic leukemia reported by Goodman et al.[2] no improvement was obtained in six in an advanced stage of the disease. In six earlier cases the results were regarded as comparable to those following irradiation. Jacobson et al.[3] similarly obtained remissions in three of seven cases of chronic myeloid leukemia. In seven of eight cases of chronic lymphoid leukemia one or more remissions was obtained. Five of these patients died within about a year, however, and only two survived 18 to 21 months.

In five cases of polycythemia rubra [3] favorable results were obtained which may prove comparable to those following radio-active phosphorus.

In other diseases in which treatment with nitrogen mustards has been reported, little or no benefit has been obtained. These include nine cases of acute or subacute leukemia, two of multiple myeloma, one of follicular lymphoblastoma, and about 10 cases of other neoplasms of various types. The number of these cases is obviously too small to warrant any conclusions and further study is needed.

Only tentative conclusions can be drawn from the work thus far reported. It does suggest that the nitrogen mustards deserve a place, although probably a subsidiary one, in the treatment of Hodgkin's disease and lymphosarcoma and possibly in some cases of chronic leukemia. The manifest advantages the nitrogen mustards possess over radiation in the treatment of Hodgkin's disease are: Favorable results are obtained more promptly; the mustards are effective in some patients who have become resistant to irradiation and possibly may restore sensitiveness to irradiation in certain cases; the gastro-

intestinal disturbances caused by the treatment are usually less disturbing; and the treatment should be less expensive. It is possible, but not yet demonstrated, that if used as a supplement to radiation, they may increase its effectiveness. The remissions obtained, however, are usually much briefer, and injury to hemopoietic tissue is more severe and much more difficult to control. Neither procedure cures the disease but merely procures temporary remissions.

Many substances similar in chemical structure to these mustards are available or can be easily synthesized, and the hope is warranted that one may be found which is more effective and less toxic. Such a substance, however, would have to possess a remarkable degree of specificity in its action if it were to eliminate the lymphocytes in these neoplastic tissues without simultaneously injuring the normal lymphocytes and marrow cells.

Until much more experience has been gained, irradiation (as long as it is effective) remains the preferable treatment for general use.

P. W. C.

REVIEWS

Experimental Basis for Neurotic Behavior: Origin and Development of Artificially Produced Disturbances of Behavior in Dogs. By W. HORSLEY GANTT, M.D., Associate in Psychiatry and Head of the Pavlovian Laboratory, The Johns Hopkins Hospital. 211 pages; 26.5 × 18.5 cm. Paul B. Hoeber, Incorporated, New York. 1944. Price, $4.50.

Dr. W. Horsley Gantt, who has for some years been Head of the Pavlovian Laboratory of the Johns Hopkins University, presents in this volume the results of 12 years of research following leads and methods described by the great Russian physiologist Ivan P. Pavlov. Dr. Gantt, who is both a trained psychiatrist and a psychologist, spent about three years in Pavlov's Laboratory, and in 1928 translated his lectures on Conditioned Reflexes. The present volume can be considered both a beginning and a culmination. It is the culmination of a series of carefully controlled experiments demonstrating that nervous disorders can be accurately observed, predicted and to an extent controlled. It is a beginning in that it represents a methodology which in its application to humans is still in its infancy. As the author points out the study of conditioned reflexes is not the only objective, scientific method, but it is one of very few such methods which have been applied to the study of the human mind. This book is in no sense a popular presentation. It represents an important landmark in scientifically bridging the gap between neurophysiology and psychiatry. In fact it was because of the work presented in this volume that the author was granted the Lasker Award in Mental Hygiene in 1946.

H. W. N.

A History of Medicine. By DOUGLAS GUTHRIE, M.D., F.R.C.S.Ed., F.R.S.E. With an Introduction by Samuel C. Harvey, M.D., F.A.C.S., William H. Carmalt, Professor of Surgery, Yale University School of Medicine. 448 pages; 24 × 16 cm. J. B. Lippincott Company, Philadelphia. 1946. Price, $6.00.

Every physician should have some knowledge of the history of his profession. The choice of which one to study or possess is a difficult one since no one, in writing a history of medicine, can stress exactly the points each reader might be most interested in. Dr. Guthrie of Edinburgh has produced both a scholarly and a highly readable volume. He quotes so much from his sources that in this respect it is a better source book than many histories. The sources are adequately cited on each page, at the end of each chapter, and in a classified bibliography given at the end of the book, so that the reader may pursue further any topic that he may become interested in. The reviewer recommends this book as a useful addition to the library of any physician.

H. W. N.

A Textbook of Medicine. Edited by RUSSELL L. CECIL, A.B., M.D., Sc.D., Professor of Clinical Medicine, Cornell University Medical College; with assistance of WALSH MCDERMOTT, M.D., Associate Professor of Medicine, Cornell University Medical College. Associate Editor for Diseases of the Nervous System: HAROLD G. WOLFF, M.D., Associate Professor of Neurology, Cornell University Medical College. Seventh Edition, xxxiii, 1730 pages, index, with 224 illustrations. W. B. Saunders Co., Philadelphia and London. 1947. Price, $10.00.

The seventh edition of this very popular textbook will be gratefully received by the medical public. The general plan of organization is unchanged; the list of contributors includes many of the leading teachers in the United States.

Sixteen subjects have been newly introduced and more than 50 articles have been prepared anew because of death or retirement of contributors to earlier editions.

The text is again arranged in two columns, which makes for comfort in reading. Illustrations are excellent, especially those in color.

In general, subject matter is very well presented, but some objections might be registered to a few articles. The discussion of the treatment of diabetic acidosis leaves much to be desired, though most of the section on diabetes is interesting and very well presented. The dose of insulin recommended for treatment of coma is inadequate, and the author advises against gastric lavage or aspiration. He also permits catheterization of the comatose patient, and suggests administration of a large quantity of glucose intravenously, without considering the level of blood sugar.

The new edition will no doubt continue to serve as the principal medical text for many medical students and in the libraries of many practitioners. It is encouraging to see this important book being kept abreast of recent advances.

T. N. C.

BOOKS RECEIVED

Books received for August are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Communal Sick-Care in the German Ghetto. By JACOB R. MARCUS, Ph.D., Adolph S. Ochs Professor of Jewish History, Hebrew Union College. 335 pages; 23.5 × 15.5 cm. 1947. The Hebrew Union College Press, Cincinnati. Price, $4.00.

Endocrinology of Neoplastic Diseases. A Symposium by Eighteen Authors. Editors: GRAY H. TWOMBLY, M.D., and GEORGE T. PACK, M.D. 392 pages; 24.5 × 16.5 cm. 1947. Oxford University Press, New York. Price, $11.00.

The Engrammes of Psychiatry. By J. M. NIELSEN, B.S., M.D., F.A.C.P., Associate Clinical Professor of Neurology and Psychiatry, School of Medicine, University of Southern California, etc., and GEORGE N. THOMPSON, A.B., M.D., Formerly Chief of Psychiatric Service, Los Angeles County General Hospital, etc. 509 pages; 24 × 16 cm. 1947. Charles C. Thomas, Springfield, Illinois. Price, $6.75.

Hospital Care in the United States: A Study of the Function of the General Hospital, Its Role in the Care of All Types of Illness, and the Conduct of Activities Related to Patient Service, with Recommendations for Its Extension and Integration for More Adequate Care of the American Public. By the COMMISSION ON HOSPITAL CARE. 631 pages; 24.5 × 16 cm. 1947. The Commonwealth Fund, New York. Price, $4.50.

Infant Nutrition: A Textbook of Infant Feeding for Students and Practitioners of Medicine (Fourth Edition). By P. C. JEANS, A.B., M.D., Professor of Pediatrics, College of Medicine, State University of Iowa, and WILLIAMS MCKIM MARRIOTT, B.S., M.D., Late Professor of Pediatrics, Washington University School of Medicine, etc. 516 pages; 22.5 × 14.5 cm. 1947. The C. V. Mosby Company, Saint Louis. Price, $6.50.

May's Manual of the Diseases of the Eye: For Students and General Practitioners (Nineteenth Edition). Revised and Edited by CHARLES A. PERERA, M.D., Assistant Clinical Professor, College of Physicians and Surgeons, Columbia University, New York, etc. 521 pages; 20 × 14 cm. 1947. The Williams & Wilkins Company, Baltimore. Price, $4.00.

The Medical Writings of Anonymous Londinensis. By W. H. S. JONES, Litt.D., F.B.A. 168 pages; 22 × 14 cm. 1947. Cambridge University Press, New York. Price, $2.75.

Nursing. By LULU K. WOLF, R.N., B.S., M.P.H., Professor of Nursing, Vanderbilt University School of Nursing. 534 pages; 22 × 15.5 cm. 1947. D. Appleton-Century Company, Incorporated, New York. Price, $3.50.

Recent Advances in Endocrinology (Sixth Edition). By A. T. CAMERON, C.M.G., M.A., D.Sc. (Edin.), F.R.I.C., F.R.S.C., Professor of Biochemistry, Faculty of Medicine, University of Manitoba, etc. 443 pages; 21 × 13.5 cm. 1947. The Blakiston Company, Philadelphia. Price, $6.00.

Specialties in Medical Practice (loose leaf) (Renewal pages for Volume I and Volume II). EDGAR VAN NUYS ALLEN, M.D., Editor, Chief of a Section in the Division of Medicine, The Mayo Clinic, Rochester, etc. With a Foreword by DONALD C. BALFOUR, M.D., F.A.C.S., F.R.C.S. (England), R.F.A.C.S., Consultant in Surgery, The Mayo Clinic, etc. 63 loose-leaf pages; 25 × 18 cm. 1947. Thomas Nelson & Sons, New York. Price, $2.50 for renewal pages.

Synopsis of Allergy (Second Edition). By HARRY L. ALEXANDER, A.B., M.D., Professor of Clinical Medicine, Washington University School of Medicine, Saint Louis, etc. 255 pages; 20 × 13 cm. 1947. The C. V. Mosby Company, Saint Louis. Price, $3.50.

COLLEGE NEWS NOTES

The American College of Physicians' Postgraduate Courses

The Bulletin of Postgraduate Courses was published and distributed to members of the College during the month of July, giving adequate time for the arrangement of plans and the consummation of registrations. Physicians, however, were rather slow in registering during the summer months and the Committee on Postgraduate Courses believes that courses should not be scheduled in the future before the first of October, whereas this year, the first three courses, namely, Internal Medicine at the University of Pittsburgh, Psychosomatic Medicine at the University of Colorado, and Mechanics of Disease at the Peter Bent Brigham Hospital, Boston, were scheduled in early September but did not enjoy maximal registration as probably would have been the case had these courses been scheduled later in the autumn. As a matter of fact, the registration for the course in Psychosomatic Medicine was inadequate and the course was cancelled with deep regret, because of its excellence. An adequate, though not maximal, registration developed for Courses 1, 3 and 4. For Course 5, Physiological Basis of Internal Medicine, at the University of Pennsylvania Graduate School of Medicine under Dr. Julius Comroe, Jr., new on the College schedule, there was a phenomenal demand. The place of meeting was changed from the Medical Laboratories of the University of Pennsylvania to the large auditorium of the University Museum, and more than 150 physicians were in attendance.

Remaining Courses on Autumn Schedule

No. 6—Advanced Cardiology
Southwestern Medical College, Dallas
Dr. Tinsley R. Harrison, Director
November 3–8, 1947.

No. 7—Chemotherapy—New Drugs
Boston University School of Medicine
Dr. Chester S. Keefer, Director
November 3–8, 1947.

No. 8—Internal Medicine
University of Wisconsin Medical School, Madison
Dr. William S. Middleton, Director
November 3–14, 1947.

No. 9—Recent Advances in the Diagnosis and Treatment of Cardiovascular Disease
Massachusetts General Hospital, Boston
Dr. Paul D. White, Director
November 10–22, 1947.

No. 10—Gastro-enterology
Graduate Hospital of the University of Pennsylvania, Philadelphia
Dr. Henry L. Bockus, Director
November 17–26, 1947.

No. 11—Cardiovascular Disease
Yale University School of Medicine, New Haven
Dr. H. M. Marvin, Director
December 1–6, 1947.

No. 12—General Medicine
University of Texas School of Medicine, Galveston
Dr. Charles T. Stone, Director
December 1–13, 1947.

Course 9 has been filled to capacity for many weeks.

These are all exceedingly fine courses, and accommodations are available at this time in all except Course 9.

Autumn Meeting, Board of Regents and Committees

The regular autumn meeting of the Board of Regents and of the standing committees of the College will be held at the College Headquarters, Philadelphia, on Saturday and Sunday, November 22–23, 1947.

The Committee on Credentials will consider at this meeting only those candidates who were formally proposed and whose credentials were completely filed not later than September 23, 1947.

All matters requiring the attention of the Board of Regents should be submitted well in advance of November 21.

Hotel Accommodations, the San Francisco Annual Session, April 19–23, 1948

Many physicians are already desiring to make hotel reservations for the 29th Annual Session of The American College of Physicians at San Francisco. There are adequate hotel rooms available but there is no single hotel large enough to serve as the primary headquarters and to accommodate the bulk of the College members. Therefore, a group of "Official Hotels" has been selected and is herewith published. All hotels are reasonably convenient to the Civic Auditorium where meetings will be held.

It is obviously necessary that the College must be able to guarantee accommodations for the speakers on the program, distinguished guests, Officers, Regents and Governors. For this purpose the Fairmont and Mark Hopkins Hotels have been selected and no direct reservations are available there. The Executive Secretary of the College will make reservations for the above group, on request, at these hotels.

The Whitcomb Hotel has been assigned to the technical exhibitors, through the Medical Exhibitors Association. All technical exhibitors should apply for accommodations at the Whitcomb through the Medical Exhibitors Association.

Physicians, their families and friends may obtain accommodations at the following hotels by writing directly to the hotel, giving, specifically, the type of accommodation desired, the date of arrival, the date of departure and clearly identifying themselves with the College and this meeting. The absence of any quoted rates for single rooms indicates the hotel has guaranteed no single rooms. The various classes, A, B and C, in many instances indicate only comparisons in sizes, for many of the Class B hotels, though smaller, are comparable with the Class A hotels.

"Official Hotels," San Francisco Meeting

Class A Rating	Rates			
	Single	Double	Twin	Suites
The Clift Hotel Mr. Joseph Herlicy Geary & Taylor Sts.		$7.00–9.00	$8.00–12.00	$20.00–30.00
Palace Hotel Mr. Edmond A. Rieder Market & New Montgomery Sts.		8.00–11.00	9.00–12.00	18.00–35.00
St. Francis Hotel Mr. Dan E. London Union Square		8.00–9.50	8.00–14.00	2-room units, with 1 bath, 18.00–20.00
Sir Francis Drake Hotel Mr. Clifford Shea 450 Powell St.	$6.00–8.00	8.00–10.00	9.00–11.00	
Class B Rating				
Bellevue Hotel Mr. J. Paul Jones Geary at Taylor Sts.		6.00	6.50	10.00
Californian Hotel Mr. P. T. Loud 405 Taylor St.	3.00	5.25	6.00	12.00
Canterbury Hotel Mr. Howard M. Hall 750 Sutter St.		5.00–6.00	6.00–7.00	
Chancellor Hotel Mr. V. Jones 433 Powell St.		5.00	6.00	
Drake-Wiltshire Hotel Mr. Walter R. Bald 340 Stockton St.	2.50–3.00	4.00–5.00	6.00	
Embassy Hotel Mr. George Savy 610 Polk St.		4.00	4.00	
Manx Hotel Mr. George S. Schreiner 225 Powell St.	3.00–3.50	4.00–4.50	5.00–6.00	
Maurice Hotel Mr. Alex Hoffer 761 Post St.		5.00	6.00	10.00
Stewart Hotel Mr. Kenneth A. Stewart 351 Geary St.		4.00–4.50	4.50–5.00	2-room units, with 1 bath, 8.00

"Official Hotels," San Francisco Meeting—Continued

Class C Rating	Rates			
	Single	Double	Twin	Suites
Barclay Hotel Mr. Gabriel Bes 235 O'Farrell St.	2.50	3.00	3.50	
Brayton Hotel Mr. Ernest Louvau 50 Turk St.		3.50–4.00	5.00	2-room units, with 1 bath, 6.50–8.00
Cartwright Hotel Mr. Irving Edelman 524 Sutter St.		4.00	4.50	
Columbia Hotel Mr. Alan Strong 411 O'Farrell St. at Taylor		3.50	3.50	
Commodore Hotel Miss Tessie Turner 825 Sutter St.	Rates not quoted			
Devonshire Hotel Mr. Frank Benadom 335 Stockton St.	2.50	3.50–4.50	4.50–5.00	
El Cortez Hotel Mr. W. H. Sawtelle 550 Geary St.	3.50–5.00	4.50–6.00	6.00–7.00	
Fielding Hotel Mr. Ernest F. Peterson Geary at Mason Sts.		5.00	6.00	
Keystone Hotel Mr. Glen Gall 54 Fourth St.	3.00	3.50	5.00	
Lankershim Hotel Mr. S. D. Riddle 55 Fifth St.		3.50		
Lombard Hotel Miss Tessie Turner 1015 Geary St.	Rates not quoted			
New Alden Hotel Mr. J. A. Warren 333 Fulton St.		2.50–3.50		3-room units, with 1 bath, 4.00 4-room units, with 1 bath, 4.50
Olympic Hotel Mr. M. H. Lehr 230 Eddy St.		4.00–5.00	4.50–5.50	
Pickwick Hotel Mr. Joseph M. Lawrence 5th & Mission Sts.		4.00–5.00	4.50–5.50	

"Official Hotels," San Francisco Meeting—Continued

Class C Rating	Rates			
	Single	Double	Twin	Suites
Powell Hotel Mr. Loyal A. Hobson 17 Powell St.		4.00		3-room units, with 1 bath, 5.00 4-room units, with 1 bath, 6.00
Roosevelt Hotel Mr. Robert R. Vayssie 240 Jones St.	3.00–3.50	3.50–4.00		
Senate Hotel Mr. Hugo Jensen 467 Turk St.		3.00		3-room units, with 1 bath, 4.00 4-room units, with 1 bath, 5.00–6.00
Senator Hotel 519 Ellis St.		3.00	4.00	
Shaw Hotel Mr. C. J. Murphy Market & McAllister Sts.	3.50	5.00	6.00	
Washington Hotel Mr. D. Fitzgerald Grant Ave. & Bush St.		4.00–5.00	4.50–5.50	

Specialty Board Announcements

The American Board of Pediatrics, Inc., will hold oral examinations on December 5, 6, and 7, 1947, at Dallas, Tex.

The American Board of Radiology will hold an examination at the Statler Hotel, Boston, Mass., November 26–30, 1947.

The American Board of Psychiatry and Neurology, Inc., has tentatively scheduled regular examination in New York City, December 15, 16, and 17, 1947. Applications for admissions to this examination closed on September 15.

In order to avoid misunderstanding regarding the allowance of one year of training credit for work in the armed forces during wartime, it should be noted that wartime, to The American Board of Psychiatry and Neurology, Inc., means V–J Day plus six months. Therefore, men who entered the service on V–J Day would be allowed six months' credit. Those men who entered the armed forces after February of 1946 will not be granted credit toward the training requirements, unless they were residents in hospitals approved by this Board for residency training. If they have practiced psychiatry or neurology during this time, however, it is probable that this will be counted toward the experience requirements.

The Royal College of Physicians and Surgeons of Canada will hold oral and clinical examinations for the Diploma of Fellow, in Toronto, November 24–27, 1947.

From December 1 to 6, 1947, the American Trudeau Society will offer in San Francisco, for physicians in the states of California, Washington, Oregon, Idaho, and Nevada, a postgraduate course on diseases of the chest. Registration in this course will be limited to 30 internists interested in this field. The tuition fee will be Fifty Dollars. Information concerning registration and the program may be obtained from Cameron St. C. Guild, Executive Secretary, 1790 Broadway, New York 19, N. Y.

The course will be sponsored by the University of California Medical School, the Stanford University School of Medicine, and the San Francisco Department of Health. The Regional Sub-committee includes Dr. Carl R. Howson, F.A.C.P., Los Angeles; Dr. Sidney J. Shipman, F.A.C.P., San Francisco; and Dr. Harold G. Trimble, F.A.C.P., Oakland.

This is the third in a series of postgraduate courses presented by the Society. The most recent course was that given July 28–August 9 at Denver, Colo. The University of Colorado School of Medicine, Dr. Ward Darley, Jr., F.A.C.P., Dean, participated in this course, and the Regional Sub-committee included Dr. James J. Waring, F.A.C.P., Denver, as Chairman.

The American Association for the Study of Goiter, of which Dr. J. H. Means, F.A.C.P., Boston, is President, will hold its annual session at Toronto, Canada, May 6–8, 1948. The Van Meter Prize Award of $300, and two honorable mentions will then be made for the best essays on original work on thyroid problems. To be eligible, essays must be typed in English, double spaced, not more than 3,000 words, and submitted to Dr. T. C. Davison, Corresponding Secretary, 207 Doctors' Bldg., Atlanta 3, Ga., before February 1, 1948.

The College takes pleasure in announcing that on August 20, 1947, Dr. Donald Maclean Willson, F.A.C.P., Milwaukee, Wis, became a Life Member of the College.

Dr. Thomas Parran, F.A.C.P., Surgeon General of the United States Public Health Service, has been awarded the Typhus Commission Medal for his outstanding and inspiring contributions to the work of the Commission, both in the United States and overseas.

Dr. Henry O. Colomb, F.A.C.P., New Orleans, has recently been appointed to the Professorship of Psychiatry in the Louisiana State University School of Medicine.

Edwin P. Jordan, M.D., F.A.C.P., formerly of Chicago where he served as Associate Editor of the Journal of the American Medical Association and as a writer for the Chicago Sun Syndicate, has become Director of Medical Education and the Bunts Educational Institute of the Cleveland Clinic. In this new position Dr. Jordan will direct the institute's increased activities in postgraduate courses and fellowship training, as well as the lecture courses for practicing physicians.

Colonel William D. Graham (MC), USA, F.A.C.P., has been appointed Chief of the Hospital Division in the Surgeon General's Office.

Dr. James R. Reuling, F.A.C.P., Bayside, N. Y., has been elected President of the National Tuberculosis Association; Dr. Horton C. Hinshaw, F.A.C.P., Rochester, Minn., has been designated as President-Elect, and Dr. David A. Cooper, F.A.C.P., Philadelphia, Secretary-Treasurer.

Dr. John S. La Due, F.A.C.P., New York City, has been elected Secretary of the American Federation for Clinical Research.

Dr. Walter L. Bierring, F.A.C.P., Commissioner, State Department of Health, Des Moines, Iowa, has contributed to the College Library of Publications by Members a copy of the new sixth edition of Rypins' "Medical Licensure Examinations," which has been prepared under his editorial direction and recently published by J. B. Lippincott Company, Philadelphia.

Dr. John M. Swan, Rochester, N. Y., has donated to the American College of Physicians Library a copy of the "Transactions of the John Guiteras Medical Society of Undergraduates of the University of Pennsylvania," for the year 1892–93. Dr. Swan was the President of that Society during his third year in the Medical School of the University of Pennsylvania, and this publication is a worthy example of the work of the undergraduate group under the inspiration of a great leader of his day.

Neurologists and Psychiatrists in the American College of Physicians

A recent survey of the membership of the American College of Physicians reveals that there are 67 Associates and 215 Fellows, or a total of 285, who give neurology, psychiatry, or neuropsychiatry as their primary specialties. There is an almost equal number who give one of these specialties as their secondary field of interest.

The Chief Medical Director of the Veterans Administration Reports

Dr. Paul R. Hawley, F.A.C.P., Chief Medical Director of the Veterans Administration, who has recently been made an Honorary Fellow of the American Association for the Surgery of Trauma, in a report to the Branch Medical Directors, Managers of Hospitals and Centers, Managers of Regional Offices, and Veterans Administration Offices having Medical Divisions, on September 2, 1947, reported, in part, as follows: "While much still remains to be done, we may well be gratified with our achievements during this past year. Quantitative measurements cannot begin to tell the story, for our greatest accomplishment has been the marked progress towards our goal of providing all eligible beneficiaries with the best possible medical service in accordance with the highest current professional standards. The human suffering that has been avoided by more rapid and more effective therapy, the achievements of the mental hygiene program in staving off mental illness, and of the medical rehabilitation program in rebuilding shattered lives, the changing emphasis in neuropsychiatric hospitals from custodial care to genuine treatment, and many other equally significant advances—none of these can be calculated in cold statistical terms.

"However, even when judged by quantitative standards alone, our achievements during the past fiscal year have been impressive. A total of 386,614 veterans were admitted to our hospitals during the Fiscal Year 1947, compared to 271,299 for the previous year. VA patients hospitalized during the year at any one time averaged 98,600, compared to 78,900 during the previous year, an increase of 25 per cent. Our hospital plant had 108,225 authorized beds and 101,273 available beds as of June 30, 1947, compared to 91,675 authorized and 87,369 available beds as of June 30, 1946. A total of 2,744,602 individuals were given medical examinations and 564,171 individuals were given dental examinations during Fiscal Year 1947, a marked increase over the comparable figures of 1,036,634 individuals examined medically and 85,537 individuals given dental examinations during the preceding year. A similar growth was manifested in medical and dental out-patient treatments."

American Academy of General Practice

At the 1947 Atlantic City Convention of the American Medical Association, the American Academy of General Practice was founded. The purposes of this new organization, as stated in the constitution, are to promote and maintain high standards in the general practice of medicine and surgery; to encourage study for general practitioners; to encourage young people to qualify for general practice; to maintain and enhance the prestige of general practice; and to advance medical science and health. This organization is not of the nature of a certifying or accrediting board. Dr. Paul A. Davis, Akron, Ohio, has been elected first President of the Academy. Initiation fee is $10.00 and dues are $15.00 per year.

Programs of Recent Regional Meetings

At the time of writing, a number of Regional Meetings of the College have been held for which information concerning registration has not yet been received. Accordingly, the programs of these meetings are here presented in summarized form without comments.

Western Pennsylvania

This meeting was held at Pittsburgh on Wednesday, September 10, under the Governorship of R. R. Snowden, M.D., F.A.C.P. The morning program consisted of a symposium on diseases of the liver in which Campbell Moses, M.D. (by invitation), spoke on "The Physiology of the Diseased Liver"; John F. Beauregard, M.D. (by invitation), on "Infectious Hepatitis"; and Morris Hershenson, M.D., F.A.C.P., on "The Clinical Use of Liver Function Tests." These speakers were all from the University of Pittsburgh School of Medicine. The afternoon session took place at the Buhl Planetarium and Hall of Science and included a demonstration of the planetarium projector by Arthur L. Draper, Ph.D., Director of the Planetarium, and a demonstration and an exhibit on nuclear physics and nuclear energy. Cocktails and a banquet at the Pittsburgh Athletic Association Annex were followed by a musical program and brief talks by distinguished guests, among whom were listed Dr. Walter W. Palmer, New York City, President-Elect of the College; Dr. A. B. Brower, Dayton, Ohio, Regent of the College; and Dr. M. A. Blankenhorn and Dr. D. A. MacGregor, College Governors for Ohio and West Virginia, respectively.

Oklahoma

On Saturday, September 20, 1947, this meeting was held at Oklahoma City, Wann Langston, M.D., F.A.C.P., Governor, acting as General Chairman. The following papers were presented by Fellows of the College in the Morning Session at the University of Oklahoma Medical School Building: "Gaseous Exchange and Fluid Mobilization," by Edward C. Mason, Oklahoma City; "The Use of Diuretics," by John B. Morey, Ada; "Cerebral Manifestations of Digitalis Intoxication," by Russell C. Pigford, Tulsa; "Adreno-Cortical Syndromes," by Henry C. Turner, Oklahoma City. Also included in the Morning Session were a clinic—"Peripheral Vascular Disease"—by George N. Barry, M.D., F.A.C.P., and John Powers Wolff, M.D. (by invitation), both of Oklahoma City, and a panel discussion on Chemotherapy, of which Dr. Langston was moderator and in which the following subjects were discussed by Fellows from Oklahoma City: "Sulphonamides," by R. Q. Goodwin; "Penicillin in Infections Other than Syphilis," by W. W. Rucks, Jr.; "Streptomycin in Tuberculosis," by Floyd Moorman. Phyllis Jones, M.D. (by invitation), Oklahoma City, and E. Rankin Denny, M.D., F.A.C.P., Tulsa, also participated in the discussion, their sub-

jects being "Penicillin in Syphilis" and "Streptomycin in Infections Other than Syphilis," respectively. Luncheon was served at the University Hospital. The Afternoon Session included a talk by Dr. Hugh J. Morgan, President of the College, and the following papers: "Some Problems in Nutrition," by Paul B. Cameron, M.D. (Associate), Prior; "Infectious Hepatitis," by Charles J. Roberts, M.D. (Associate), Enid; "The Present-Day Management of Peptic Ulcer," by Harry A. Daniels, M.D., F.A.C.P., Oklahoma City; "X-Ray Diagnosis of Peptic Ulcer," by John R. Danstrom, M.D. (by invitation), Oklahoma City. Following this there was a clinical pathological conference by Emil J. Palik, M.D. (by invitation), Tulsa. Open discussion was invited. At the dinner in the evening at the Hotel Biltmore, Dr. Wann Langston was Toastmaster and Dr. Hugh J. Morgan was Guest Speaker.

Nebraska

The Nebraska Regional Meeting took place at the Cornhusker Hotel, Lincoln, Saturday, September 20, 1947, under the Governorship of Joseph D. McCarthy, M.D., F.A.C.P., of Omaha, and with George W. Covey, M.D., F.A.C.P., acting as Chairman of the Program Committee. The following papers were presented: "Calcium, Phosphorus, and Serum Determinations as Observed at the University of Nebraska Hospital," by Esley J. Kirk, M.D., F.A.C.P., Omaha; "Treatment of Subacute Bacterial Endocarditis," by Arthur L. Smith, Jr., M.D. (Associate), Lincoln; "Spontaneous Hemopneumothorax," by W. Wayne Waddell, M.D. (Associate), Beatrice; "Arthritis in Amoebiasis," by Horace H. Zinneman, M.D. (Associate), Lincoln; "Thiouracil in the Treatment of Hypertensive Cardiovascular Disease," by Benjamin F. Wolverton, M.D., F.A.C.P., Cedar Rapids, Iowa; and "The Use and Abuse of Irradiation Therapy in the Treatment of Uterine Bleeding," by J. Marshall Neely, M.D., F.A.C.P., Lincoln. An open discussion followed. Cocktails were served in the evening. At the dinner, Dr. Joseph D. McCarthy presided, Benjamin F. Wolverton, M.D., F.A.C.P., Governor for Iowa, spoke on "Current Problems of The American College of Physicians," and R. G. Gustavson, Ph.D., Chancellor, University of Nebraska, Lincoln, talked on "The Newer Chemistry in Medicine."

Iowa

The Des Moines Club was the locus of this meeting on Saturday, September 27, 1947. The meeting was under the Governorship of B. F. Wolverton, M.D., F.A.C.P., Cedar Rapids, with George E. Mountain, M.D., F.A.C.P., Des Moines, as Chairman of the Program Committee. The program consisted of an informal luncheon and an afternoon session at which the following papers were presented by Iowa physicians: "The Prothrombin Time in Dicumarol Therapy," by Francis C. Coleman (by invitation), Des Moines; "Review of Nitrogen Mustard Therapy," by Willis M. Fowler, F.A.C.P., Iowa City; "Paroxysmal Cardiac Dyspnea," by Hyman M. Hurevitz (Associate), Davenport; "Management of Tuberculosis by the Internist," by Leon J. Galinsky (Associate), Des Moines; "The Precordial Electrocardiogram," by Lewis E. January (Associate), Iowa City; "Polyneuritis Due to Hematoporphyria," by Adolph L. Sahs, F.A.C.P., Iowa City; "Electroshock Treatments," by Frank J. Piekenbrock (Associate), Dubuque. Dr. Albert M. Snell, F.A.C.P., Rochester, Minn., was Guest Speaker, his paper being entitled, "Clinical and Psychological Consideration of Patients with Cirrhosis." Dinner was preceded by cocktails. Herman J. Smith, M.D. (Associate), Des Moines, presided for the evening session at which Walter L. Bierring, M.D., F.A.C.P., Des Moines, spoke on "The American College of Physicians in Retrospect and in Prospect," and a motion picture on Cardiology was shown.

New England

A fine program was arranged by Dr. E. L. Amidon, Governor for Vermont, for members of the College in Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island and Vermont, at Burlington, Vt., on October 14. College members in the Province of Quebec and the Maritime Provinces also were invited.

W. E. Brown, M.D., Dean of The College of Medicine of the University of Vermont, welcomed the group to the University's Fleming Museum. Papers were presented by Harris B. Shumacker, Jr., M.D. (by invitation), New Haven, on "Sympathetic Nerve Surgery: Its Usefulness and Limitations"; by Charles H. Burnett, M.D. (by invitation), Boston, on "Kidney Physiology"; by Jarrett H. Folley, M.D. (Associate), Hanover, on "Aplastic Anemia"; by I. M. Rabinowitch, M.D., F.A.C.P., Montreal, on "Relationship between Liver Function and Premature Development of Arteriosclerosis in Diabetes Mellitus"; by Walter C. Lobitz, Jr., M.D. (by invitation), Hanover, on "The Skin and Lymphoblastoma"; by James W. Culbertson, M.D. (by invitation), Boston, on "Hypertension"; by Alex. M. Burgess, F.A.C.P., Providence, on "Excessive Hypertension of Long Duration"; and by Robert D. Roach, M.D., F.A.C.P., on "Pericarditis."

The scientific session was followed by a dinner at the Ethan Allen Club, at which C. H. Beecher, M.D., F.A.C.P., Burlington, presided. The guest address was by Mr. A. E. Whiting, General Manager of *The Herald*, Montreal. The list of distinguished guests included Dr. Walter W. Palmer, New York, Dr. Reginald Fitz, Boston, Dr. Francis G. Blake, New Haven, President-Elect, First and Second Vice Presidents of the College, respectively, as well as A.C.P. Regents Charles F. Moffatt, M.D., C.M., Montreal, and Alex. M. Burgess, M.D., Providence.

Philadelphia Department of Public Health Offers Opening for Assistant Director, Medical Education

Dr. P. F. Lucchesi, Superintendent and Medical Director of the Philadelphia General Hospital, in conjunction with the Philadelphia Department of Public Health, announces an opening for an Assistant Director of Medical Education, Grade 12, $4,200–$4,800 a year and maintenance. Candidates should file applications immediately to Dr. Lucchesi at the Philadelphia General Hospital, 34th St. and Curie Ave., Philadelphia 4, Pa.

Duties: Under the direction of the Superintendent and Medical Director, to have administrative charge of, and be responsible for, the direction, assignment, instruction, training and scheduling of the work and training program for resident physicians, internes and medical and postgraduate students assigned to the hospital; to confer and advise with staff members concerning the examination, activities and performance records of this group; to prepare teaching schedules and material for lectures; to be responsible for the development of the medical education program; to make recommendations for changes and improvements in the rules, regulations, technics and procedures of the hospital; to plan, prepare and edit reports and scientific papers issued or published by the hospital; to be responsible for the handling of public relations and the preparation of reports for newspapers, periodicals and medical journals; etc.

Training and experience count four points in the qualifications; practical questions, four points; and personal interview, two points.

Minimum requirements include: An M.D. degree from an acceptable medical school; license to practice medicine in Pennsylvania; two years of experience as assistant to a Medical Director and one year of experience in a hospital administra-

tive division; thorough knowledge of the fundamental sciences underlying the practice of medicine in its various branches; thorough knowledge of the examination, diagnosis and treatment of medical and surgical cases; some experience in hospital and medical publicity work; supervisory and administrative ability; ability to plan and prepare teaching programs; editorial ability in medical publication; public speaking ability on medical educational matters; ability to meet with the public; thoroughness; tact; high moral standards; good physical condition.

New Research Director

Smith, Kline & French Laboratories

Smith, Kline & French Laboratories, Philadelphia, Pa., have announced the appointment, as Director of their Research Laboratories, of Maurice L. Moore, B.S., University of Florida, 1930; Ph.D., Northwestern University, 1934. Dr. Moore has been Assistant Director of Research of Frederick Stearns and Company. Retiring Chairman of the Division of Medicinal Chemistry of the American Chemical Society, Dr. Moore also is a Fellow of the American Association for the Advancement of Science and a member of the American Institute of Chemists, American Pharmaceutical Association, Society of Chemical Industry, and the Pennsylvania Academy of Science. Active in the study of sympathomimetic amines, a field of interest to Smith, Kline & French for the past fifteen years, Dr. Moore has also made important discoveries in the course of studies of sulfonamides which he began some years ago as a Research Fellow in organic chemistry at Yale University.

Retirements from Service

Since the last publication of this journal, the following members of the College have been reported retired or on terminal leave (to September 12, 1947 inclusive).

Elizabeth Brakeley, Montclair, N. J. (Major, USPHS(R))
Sidney Miller, Rochester, Minn. (Major, MC, AUS)
Joseph G. Rushton, Rochester, Minn. (Capt., MC, AUS)

A.C.P. Postgraduate Courses Still Open for Registration

There remain facilities to accommodate all interested members and some qualified non-members in Course No. 10, Gastro-enterology, and in Course No. 12, General Medicine, at the Graduate Hospital of the University of Pennsylvania and the University of Texas School of Medicine, respectively. To acquaint all interested physicians with the full details of these courses, a full outline is herewith published. It is recommended, however, that anyone wishing to register communicate immediately with

E. R. Loveland, Executive Secretary
The American College of Physicians
4200 Pine Street
Philadelphia 4, Pa.

COURSE NO. 10—GASTRO-ENTEROLOGY

(November 17–26, 1947)

Graduate Hospital of the University of Pennsylvania and the Philadelphia General Hospital, Philadelphia, Pa.

HENRY L. BOCKUS, M.D., F.A.C.P., *Director*

(Minimal Registration, 50; Maximal Registration, 75)

Fee: A.C.P. Members, $45.00. Non-Members, $90.00

Officers of Instruction

Thomas P. Almy, M.D., Assistant Professor of Medicine, Cornell University College of Medicine, New York, N. Y.

William Bates, M.D., F.A.C.S., Professor of, and Vice Dean for, Surgery, University of Pennsylvania Graduate School of Medicine.

Joseph T. Beardwood, Jr., M.D., F.A.C.P., Professor of Diseases of Metabolism, University of Pennsylvania Graduate School of Medicine.

Lawrence H. Beizer, M.D., F.A.C.P., Instructor in Medicine, University of Pennsylvania Graduate School of Medicine.

Samuel Bellet, M.D., F.A.C.P., Assistant Professor of Cardiology, University of Pennsylvania Graduate School of Medicine.

J. Edward Berk, M.D., F.A.C.P., Assistant Professor of Medicine, Temple University School of Medicine.

Henry L. Bockus, M.D., F.A.C.P., Professor of Gastro-enterology, University of Pennsylvania Graduate School of Medicine.

Julius H. Comroe, Jr., M.D., F.A.C.P., Professor of Physiology and Pharmacology, University of Pennsylvania Graduate School of Medicine.

George Eaton Daniels, M.D., Clinical Professor of Psychiatry, Columbia University College of Physicians and Surgeons, New York, N. Y.

David L. Drabkin, M.D., Professor of Physiological Chemistry, University of Pennsylvania Graduate School of Medicine.

William E. Ehrich, M.D., Professor of Pathology, University of Pennsylvania Graduate School of Medicine.

L. Kraeer Ferguson, M.D., F.A.C.S., Professor of Surgery, University of Pennsylvania Graduate School of Medicine.

Arthur Finkelstein, M.D., Assistant Professor of Radiology, University of Pennsylvania Graduate School of Medicine.

Herbert S. Gaskill, M.D., Associate in Psychiatry and in Medicine, University of Pennsylvania School of Medicine.

W. Paul Havens, Jr., M.D., Associate Professor of Preventive Medicine and Associate in Medicine, Jefferson Medical College.

Herbert R. Hawthorne, M.D., F.A.C.S., Professor of Clinical Surgery, University of Pennsylvania Graduate School of Medicine.

J. Warren Hundley, Jr., M.D., F.A.C.P., Instructor in Gastro-enterology, University of Pennsylvania Graduate School of Medicine.

Thomas A. Johnson, M.D., F.A.C.P., Associate Professor of Gastro-enterology, University of Pennsylvania Graduate School of Medicine.

George P. Keefer, M.D., Instructor in Radiology, University of Pennsylvania Graduate School of Medicine.

Mack Lopusniak, M.D., Fellow in Gastro-enterology, University of Pennsylvania Graduate School of Medicine.

Balduin Lucké, M.D., Professor of Pathology, University of Pennsylvania School of Medicine.

Thomas E. Machella, M.D., Assistant Professor of Medicine and Instructor in Physiology, University of Pennsylvania School of Medicine.

Thomas M. McMillan, M.D., F.A.C.P., Associate Professor of Cardiology, University of Pennsylvania Graduate School of Medicine.

Merle M. Miller, M.D., F.A.C.P., Assistant Professor of Allergy, University of Pennsylvania Graduate School of Medicine.

T. Grier Miller, M.D., F.A.C.P., Professor of Medicine, University of Pennsylvania School of Medicine.

James F. Monaghan, M.D., Assistant Professor of Gastro-enterology, University of Pennsylvania Graduate School of Medicine.

John R. Neefe, M.D., Associate in Medicine, University of Pennsylvania School of Medicine.

Wilbur W. Oaks, M.D., Associate in Surgery, University of Pennsylvania Graduate School of Medicine.

Johannes F. Pessel, M.D., F.A.C.P., Assistant Professor of Gastro-enterology, University of Pennsylvania Graduate School of Medicine.

Edward C. Raffensperger, M.D., Fellow in Gastro-enterology, University of Pennsylvania Graduate School of Medicine.

Abraham E. Rakoff, M.D., Associate in Gynecology and Obstetrics, Jefferson Medical College; Endocrinologist, Department of Clinical Laboratories, Jefferson Medical College Hospital.

I. S. Ravdin, M.D., F.A.C.S., John Rhea Barton Professor of Surgery and Director of the Harrison Department of Surgical Research, University of Pennsylvania School of Medicine.

Joseph A. Ritter, M.D., Associate Professor of Pediatrics, University of Pennsylvania Graduate School of Medicine.

Maurice M. Rothman, M.D., Associate in Gastro-enterology, University of Pennsylvania Graduate School of Medicine.

Alexander Rush, M.D., Assistant Instructor in Gastro-enterology, University of Pennsylvania Graduate School of Medicine.

Thomas S. Sappington, M.D., American College of Physicians Fellow in Gastro-enterology, University of Pennsylvania Graduate School of Medicine.

Harry Shay, M.D., Clinical Professor of Medicine, Temple University School of Medicine.

Calvin M. Smyth, Jr., M.D., F.A.C.S., Professor of Clinical Surgery, University of Pennsylvania Graduate School of Medicine.

J. Earl Thomas, M.D., Professor of Physiology, Jefferson Medical College.

Gabriel Tucker, M.D., F.A.C.S., Professor of Bronchology, Esophagology and Laryngeal Surgery, University of Pennsylvania Graduate School of Medicine.

Henry J. Tumen, M.D., F.A.C.P., Associate Professor of Gastro-enterology, University of Pennsylvania Graduate School of Medicine.

Edward Weiss, M.D., F.A.C.P., Professor of Clinical Medicine, Temple University School of Medicine.

Bernard B. Widmann, M.D., Professor of, and Vice Dean for, Radiology, University of Pennsylvania Graduate School of Medicine.

John H. Willard, M.D., F.A.C.P., Assistant Professor of Gastro-enterology, University of Pennsylvania Graduate School of Medicine.

Stewart G. Wolf, Jr., M.D., Assistant Professor of Medicine, Cornell University Medical College, New York, N. Y.

Joseph C. Yaskin, M.D., Professor of Neurology, University of Pennsylvania Graduate School of Medicine.

Harold A. Zintel, M.D., Assistant Instructor in Surgery, University of Pennsylvania School of Medicine.

David E. Zion, M.D., Instructor in Radiology, University of Pennsylvania Graduate School of Medicine.

The course is designed to give a survey of recent developments in gastroenterology. Considerable emphasis is placed on gastrointestinal physiology. The program comprises didactic presentations, conferences, case presentations and panel discussions. The teachers have been selected with care, including members of the faculty of several nearby medical schools in addition to those of the faculty of the University of Pennsylvania.

This course is scheduled for one and one-half weeks and will be concluded at noon, November 26, the day before Thanksgiving. Certain sessions will be held in the North Lecture Room of the Graduate Hospital of the University of Pennsylvania, 19th and Lombard Sts., and other sessions will be held in the auditorium of the Administration Building of the Philadelphia General Hospital, 34th St. below Spruce.

A special feature of the course will be the Eastern Pennsylvania Regional Meeting of the College on Friday afternoon, November 21, including luncheon at the College Headquarters and a scientific program, reception and dinner at the Warwick Hotel in the afternoon and evening. All members of the class are cordially invited. Dr. Hugh J. Morgan, President of the College, several members of the Board of Regents and other distinguished guests will be in attendance.

Hotel Accommodations: The Warwick Hotel, 17th and Locust Sts., Philadelphia 3, will accommodate registrants, provided that in making application they identify themselves with the College and this course. However, unless conditions change in the meantime, it will be necessary that members share large, twin-bedded rooms, due to the dearth of single rooms. Rates: Double, twin-bedded rooms, $8, $9 and $10.

Outline of Course

Monday, November 17.

A.M. Session—Philadelphia General Hospital—Auditorium, Administration Building.

8:15– 9:00 Registration.

9:00– 9:10 Assembly and Introductory Remarks.
Dr. R. C. Buerki, Dean, University of Pennsylvania Graduate School of Medicine, and Dr. Bockus.

9:10– 9:30 Pyrosis: Its Mechanism and Clinical Significance.
Dr. Tumen.

DIFFERENTIAL DIAGNOSIS OF ANGINA PECTORIS

9:30– 9:45 Mechanism of Anginoid Pain.
Dr. Comroe.

9:45–10:00 Is It True Angina Pectoris?
Dr. McMillan.

10:00–10:15 Anginoid Pain Due to Alimentary Tract Disorders.
Dr. Bockus.

10:15–10:45 Esophagoscopy in Diagnosis and Treatment of Esophageal Lesions.
Dr. Tucker.

10:45–10:55 Intermission.

10:55–11:10 Roentgen Demonstration of Esophageal Lesions and Hiatal Hernia.
Dr. Zion.

11:10–11:20 Mechanism of Development of Cardiospasm and Functional Megaesophagus.
Dr. Machella.

11:20–11:35 Diagnosis and Medical Treatment of Cardiospasm and Functional Mega-esophagus.
Dr. Willard.
11:35–11:45 Surgical Treatment of Functional Mega-esophagus.
Dr. Hawthorne.
11:45–12:00 Diagnosis and Medical Treatment of Hiatus Hernia.
Dr. Johnson.
12:00–12:10 Operation for Hiatus Hernia.
Dr. Ferguson.

CARCINOMA OF THORACIC ESOPHAGUS AND CARDIA

12:10–12:30 Clinical Aspects.
Dr. Monaghan.
12:30–12:45 Surgical Approach.
Dr. Hawthorne.

P.M. Session—The Graduate Hospital.

2:15– 3:00 Remarks on Mechanism of Abdominal Pain.
Dr. Bockus.
3:00– 3:30 Functions of the Stomach as Observed in Fistulous Human Subjects.
Dr. Wolf.
3:30– 4:00 Value of Certain Gastric Analysis Procedures (Histamine, Caffeine and Insulin Tests).
Dr. Berk.
4:00– 4:10 Intermission.
4:10– 5:20 Presentation of Patients, Illustrating Current Problems in Diagnosis and Therapy.
Dr. Bockus and Colleagues.

Tuesday, November 18.

A.M. Session—Philadelphia General Hospital.

9:00– 9:30 Gastroscopy and X-Ray in the Diagnosis of Chronic Gastritis.
Drs. Monaghan and Finkelstein.
9:30–10:00 Incidence and Clinical Importance of Achlorhydria.
Dr. Johnson.
10:00–10:20 Mechanism of Secretory and Motor Behavior of Stomach in Duodenal Ulcer Disease.
Dr. Shay.
10:20–10:40 The Personality Pattern and the Role of Emotional Tension in the Patient with Duodenal Ulcer.
Dr. Gaskill.
10:40–11:00 Etiology and Pathogenesis of Duodenal Ulcer.
Dr. Tumen.
11:00–11:10 Intermission.

DIAGNOSIS OF DUODENAL ULCER

11:10–11:30 Clinical Aspects.
Dr. Shay.
11:30–11:45 X-Ray.
Dr. Finkelstein.

THERAPY OF UNCOMPLICATED DUODENAL ULCER

11:45–12:15 Principles of Therapy in Healing of Active Ulcer.
Dr. Willard.

12:15–12:30 Future of Hormones in Ulcer Therapy.
Dr. Shay.
12:30–12:40 Place of Protein Hydrolysates.
Dr. Sappington.
12:40– 1:00 Cause and Prevention of Recurrences.
Dr. Johnson.
P.M. Session—Philadelphia General Hospital.

STATUS OF INTERRUPTION OF VAGUS FIBERS IN PEPTIC ULCER THERAPY

(Panel Discussion)

2:15– 2:30 Physiologic Basis.
Dr. Comroe.
2:30– 2:40 Possible Indications.
Dr. Bockus.
2:40– 2:50 Is Complete Vagotomy Easy of Accomplishment?
Dr. Hawthorne.
2:50– 3:00 Methods of Determining Efficiency of Operation.
Dr. Berk.
3: 00– 3:15 Results: Healing of Ulcer and Recurrences.
Dr. Tumen.
3:15– 3:25 Undesirable Side Effects and Their Management.
Dr. Machella.
3:25– 3:40 Questions and Answers.
3:40– 4:00 Intermission.

DIFFERENTIAL DIAGNOSIS OF BENIGN AND MALIGNANT GASTRIC ULCER

4:00– 4:15 The Pathologist's Viewpoint.
Dr. Ehrich.
4:15– 4:45 Complementary Value of Gastroscopy and X-Ray.
Drs. Monaghan and Finkelstein.

MANAGEMENT OF GASTRIC ULCER

4:45– 5:00 The Clinician's Viewpoint.
Dr. Bockus.
5:00– 5:15 The Surgeon's Viewpoint.
Dr. Smyth.

Wednesday, November 19.

A.M. Session—Philadelphia General Hospital.
9:00– 9:15 Indications for Subtotal Gastrectomy in Peptic Ulcer.
Dr. Johnson.
9:15– 9:30 Surgical Principles Involved and Results of Subtotal Gastrectomy.
Dr. Ferguson.

PEPTIC ULCER AND PYLORIC OBSTRUCTION

9:30– 9:50 Manner of Development of Hypochloremia, Alkalosis and Hyperazotemia.
Dr. Drabkin.
9:50–10:05 Therapeutic Regimen and Decision for or against Operation.
Dr. Willard.

MASSIVE BLEEDING FROM UPPER GASTROINTESTINAL TRACT

10:05–10:30 Outline of Initial Therapy, Emphasizing Differential Diagnosis.
Dr. Tumen.
10:30–10:40 Mechanism of Development of Hyperazotemia and Its Prognosis.
Dr. Bockus.
10:40–10:50 Dietary Management of Bleeding Peptic Ulcer.
Dr. Johnson.
10:50–11:00 When to Operate.
Dr. Monaghan.
11:00–11:10 Intermission.
11:10–11:30 Remarks on Non-operative Treatment of Perforated Peptic Ulcer.
Dr. Bockus.
11:30–11:50 Surgery of Perforated Ulcer: Results.
Dr. Ravdin.
11:50–12:10 Diagnosis and Management of Gastrojejunal Ulcer.
Dr. T. Grier Miller.
12:10–12:30 Gastrojejunal Colic Fistula.
Dr. Johnson.
12:30–12:50 Repair of Gastrojejunicolic Fistula: Case Presentation.
Dr. Ferguson.

P.M. Session—The Graduate Hospital.

2:30– 3:00 Differential Diagnosis of Constricting Lesions of the Pylorus: Case Presentations.
Dr. Berk.
3:00– 3:30 Present Status of Gastric Syphilis.
Dr. Monaghan.
3:30– 4:00 Intramural Gastric Tumors.
Dr. Bockus.
4:00– 4:10 Intermission.
4:10– 5:30 Presentation of Patients Illustrating Current Problems in Diagnosis and Therapy.
Dr. Bockus and Colleagues.

Thursday, November 20.

A.M. Session—Philadelphia General Hospital.

9:00– 9:20 Prognosis of Gastric Carcinoma.
Dr. Berk.
9:20–9:40 The Clinical Importance of Duodenal Diverticulitis.
Dr. Johnson.
9:40– 9:55 Surgical Management of Duodenal Diverticulosis.
Dr. Ferguson.
9:55–10:15 Postbulbar Duodenal Ulcer.
Drs. Monaghan and Finkelstein.

FUNCTIONS OF THE LIVER

10:15–10:45 Formation and Excretion of Bile.
Dr. Tumen.
10:45–10:55 Intermission.
10:55–11:25 Role of the Liver in the Metabolism of Carbohydrate, Protein and Fat.
Dr. Drabkin.
11:25–11:40 Aspiration Liver Biopsy.
Dr. Oaks.

11:40–11:55 Peritoneoscopy.
Dr. Oaks.
11:55–12:10 X-Ray Study of the Liver: Thorotrast.
Dr. Finkelstein.
12:10–12:20 Esophageal Varices.
Dr. Zion.
12:20–12:50 Differential Diagnosis of Jaundice.
Dr. Shay.

P.M. Session—The Graduate Hospital.

2:15– 3:30 Gastrointestinal Conference.
Staff.
3:30– 3:40 Intermission.

VIRUS HEPATITIS AND HOMOLOGOUS SERUM JAUNDICE

3:40– 4:10 Epidemiological and Clinical Features.
Dr. Havens.
4:10– 4:35 Pathology.
Dr. Lucké.
4:35– 5:00 Value of Liver Function Tests in Diagnosis and Prognosis.
Dr. Neefe.
5:00– 5:20 Treatment.
Dr. Berk.

Friday, November 21.

A.M. Session—Philadelphia General Hospital.

HEPATIC CIRRHOSIS

9:00– 9:20 Present Concept of Etiology of Cirrhosis.
Dr. Monaghan.
9:20– 9:30 Pathology of Hepatic Cirrhosis.
Dr. Ehrich.
9:30–10:00 Value of Liver Function Tests in Diagnosis and Prognosis.
Dr. Tumen.
10:00–10:15 The Sex Hormones in Cirrhosis of the Liver.
Dr. Rakoff.
10:15–10:30 Control of Ascites and Hemorrhage in Cirrhosis.
Dr. Bockus.
10:30–10:45 Factors Influencing Prognosis in Hepatic Cirrhosis.
Dr. Willard.
10:45–11:00 Hemochromatosis.
Dr. Berk.
11:00–11:10 Intermission.
11:10–11:25 Technical Aspects and Interpretation of Cholecystography in Gallbladder Disease.
Dr. Finkelstein.
11:25–11:45 Indications for and Interpretation of Diagnostic Biliary Drainage in Biliary Tract Disease.
Dr. Willard.
11:45–12:10 Diagnosis and Management of Acute Cholecystitis.
Dr. Berk.
12:10–12:40 Pre- and Postoperative Care of the Jaundiced Patient.
Dr. Ravdin.

12:40–12:55 Postoperative Cholangiography.
Dr. Zion.

P.M. Session.

EASTERN PENNSYLVANIA REGIONAL MEETING OF THE AMERICAN COLLEGE OF PHYSICIANS

1:00 Buffet Luncheon.
College Headquarters, 4200 Pine Street.

3:00 Scientific Program, Ballroom, Warwick Hotel, 17th & Locust Streets.
(This program, being prepared by Dr. Edward L. Bortz, Governor for Eastern Pennsylvania, will be published in special pamphlet form, and distributed in advance to all members of the class. All are cordially invited to participate in the entire Regional Meeting.)

6:30 Reception and Cocktails, Warwick Hotel.

7:15 Dinner.
Many distinguished guests, including the President of the College, Dr. Hugh J. Morgan, will be in attendance. Music and entertainment by a well known quartette.

Saturday, November 22.

A.M. Session—Philadelphia General Hospital.

SYMPOSIUM ON THE PANCREAS

9:00– 9:30 Physiology of the Pancreas.
Dr. Thomas.

TESTS FOR PANCREATIC FUNCTION

9:30– 9:45 Duodenal Intubation.
Dr. Lopusniak.

9:45–10:05 Pancreatic Serum Enzymes.
Dr. Johnson.

10:05–10:20 Chemical Analysis of Feces.
Dr. Sappington.

10:20–10:35 Microscopic Analysis of Feces.
Dr. Rothman.

10:35–10:45 Intermission.

10:45–11:05 Diagnosis and Treatment of Acute Pancreatitis.
Dr. Bockus.

11:05–11:15 Electrocardiographic Changes in Acute Pancreatitis.
Dr. Bellet

11:15–11:30 Analysis of Recent Graduate Hospital Cases of Acute Pancreatitis.
Dr. Raffensperger.

11:30–11:45 Cystic Fibrosis of Pancreas.
Dr. Ritter.

11:45–12:00 Islet Cell Tumors of the Pancreas.
Dr. Beardwood.

12:00–12:25 Diagnosis of Carcinoma of Pancreas.
Dr. Berk.

12:25–12:40 X-Ray Diagnosis of Pancreatic Carcinoma.
Dr. Finkelstein.

12:40– 1:00 Surgical Treatment of Carcinoma of Pancreas.
Dr. Ferguson.

Monday, November 24.

A.M. Session—Philadelphia General Hospital.

RECOGNITION AND CARE OF NUTRITIONAL DEFICIENCIES IN GASTROINTESTINAL DISORDERS

9:00– 9:20 Protein Deficiency.
Dr. Sappington.
9:20– 9:40 Anemia.
Dr. Beizer.
9:40–10:00 Avitaminosis.
Dr. Monaghan.
10:00–10:15 Steatorrhea.
Dr. Bockus.
10:15–10:30 Gastrointestinal Allergy.
Dr. Merle M. Miller.
10:30–10:50 Classification and Differential Diagnosis of Chronic Diarrhea.
Dr. Johnson.
10:50–11:05 Emotional Diarrhea.
Dr. Tumen.
11:05–11:15 Intermission.
11:15–11:35 Bacillary and Salmonella Infections.
Dr. Rush.
11:35–11:55 Amebic Dysentery.
Dr. Hundley.
11:55–12:10 Physiology of Defecation.
Dr. Comroe.
12:10–12:30 Functional Colonopathies.
Dr. Willard.
12:30– 1:00 Classification and Management of Constipation.
Dr. Shay.

P.M. Session—The Graduate Hospital.

2:15– 2:45 Lymphogranuloma Venereum with Colonic Involvement:
Clinical Features.
Dr. Pessel.
Roentgen Features.
Dr. Finkelstein.
2:45– 3:00 Radiation Injury of the Intestine.
Drs. Hundley and Widmann.
3:00– 3:30 Miller-Abbott Intubation in Intestinal Obstruction.
Dr. Zintel.
3:30– 3:40 Intermission.
3:40– 4:10 Parietal Abdominal Neuralgia Simulating Appendicitis.
Dr. Bates.
4:10– 5:15 Presentation of Patients Illustrating Current Problems in Diagnosis and Treatment.
Dr. Bockus and Colleagues.

Tuesday, November 25.

A.M. Session—Philadelphia General Hospital.

CHRONIC NON-SPECIFIC ENTERITIS AND ENTEROCOLITIS

9:00– 9:25 Etiology and Classification of Types.
Dr. Bockus.
9:25– 9:45 Clinical Features.
Dr. Tumen.
9:45–10:00 Roentgen Diagnosis.
Dr. Finkelstein.
10:00–10:15 Its Occurrence in Children.
Dr. Ritter.
10:15–10:30 Medical Care and Indications for Operation.
Dr. Monaghan.
10:30–10:45 Operative Procedures.
Dr. Ravdin.
10:45–11:00 Result of Operation and Prognosis.
Dr. Johnson.
11:00–11:10 Intermission.
11:10–11:30 Intestinal Tuberculosis.
Dr. Tumen.
11:30–12:00 Tumors of the Small Intestine.
Drs. Bockus and Finkelstein.
12:00–12:20 Colonic Diverticulosis.
Dr. Willard.
12:20–12:50 Diverticulitis vs. Carcinoma of the Sigmoid.
Drs. Johnson and Zion.

P.M. Session—The Graduate Hospital.

2:00– 2:30 Roentgen Studies in Intestinal Parasitosis.
Dr. Keefer.

CARCINOMA OF COLON

2:30– 2:50 Clinical Features.
Dr. Shay.
2:50– 3:05 Sigmoidoscopy.
Dr. Hundley.
3:05– 3:20 X-Ray.
Dr. Widmann.
3:20– 3:40 Operative Procedures.
Dr. Smyth.
3:40– 3:50 Intermission.
3:50– 5:00 Proctosigmoidoscopic Cinematography.
Dr. Pessel.

Wednesday, November 26.

A.M. Session—Philadelphia General Hospital.

NON-SPECIFIC ULCERATIVE COLITIS

9:00– 9:30 Classification of Types in Relation to Course of Disease.
Dr. Bockus.
9:30–10:00 Role of Psychiatric Factors.
Dr. Daniels.
10:00–10:15 Present Status of Chemotherapy and Antibiotics.
Dr. Monaghan.

10:15–10:30 Indications for Operation.
Dr. Tumen.
10:30–10:45 Operative Procedures.
Dr. Ferguson.
10:45–11:00 Prognosis.
Dr. Johnson.
11:00–11:10 Intermission.

FUNCTIONAL DISORDERS OF THE GASTROINTESTINAL TRACT OF NEUROPSYCHIATRIC ORIGIN (Panel Discussion)

11:10–11:30 Alterations in the Function of the Colon in Man under Stress.
Dr. Almy.
11:30–11:50 Functional Gastrointestinal Disturbances in Psychotic Reactions.
Dr. Yaskin.
11:50–12:10 Functional Gastrointestinal Disturbance Associated with Psychoneurotic Reactions.
Dr. Weiss.
12:10–12:40 An Appraisal of the Role of the Psyche in Gastrointestinal Disease.
Dr. T. Grier Miller.
12:40– 1:00 Questions and Answers.

COURSE NO. 12—GENERAL MEDICINE

(December 1–13, 1947)

University of Texas School of Medicine, Galveston, Texas

CHARLES T. STONE, M.D., F.A.C.P., *Director*

(Minimal Registration, 40; Maximal Registration, 50)

Fee: A.C.P. Members, $60.00. Non-Members, $120.00

Officers of Instruction

Edgar V. Allen, M.D., F.A.C.P., Associate Professor of Medicine, Mayo Foundation; Chief of a Section in the Division of Medicine, Mayo Clinic; Rochester, Minn.

John B. Barnwell, M.D., Chief, Tuberculosis Division, Veterans Administration, Washington, D. C.

Truman G. Blocker, Jr., M.D., F.A.C.S., Professor of Plastic and Maxillofacial Surgery and Director, Postgraduate Division, University of Texas School of Medicine.

Virginia Blocker, M.D., Lecturer in Medicine, University of Texas School of Medicine.

Russell S. Boles, M.D., F.A.C.P., Assistant Professor of Clinical Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pa.

Paul Brindley, M.D., F.A.C.P., Professor of Pathology, University of Texas School of Medicine; Pathologist, John Sealy Hospital.

M. Brucer, M.D., Instructor in Physiology, University of Texas School of Medicine.

George E. Burch, M.D., F.A.C.P., Associate Professor of Medicine, Tulane University of Louisiana School of Medicine, New Orleans, La.

D. Bailey Calvin, Ph.D., Professor of Biological Chemistry and Dean of Students and Curricular Affairs, University of Texas School of Medicine.

George M. Decherd, Jr., M.D., F.A.C.P., Associate Professor of Medicine and Director of Student Health Service, University of Texas.

Donald Duncan, Ph.D., Professor of Anatomy, University of Texas School of Medicine.

Jack R. Ewalt, M.D., Professor of Neuropsychiatry, University of Texas School of Medicine; Attending Neurologist and Psychiatrist, John Sealy Hospital; Director, Galveston State Psychopathic Hospital.

Chester N. Frazier, M.D., F.A.C.P., Professor of Dermatology and Syphilology, University of Texas School of Medicine; Dermatologist and Syphilologist, John Sealy Hospital.

Raymond L. Gregory, M.D., F.A.C.P., Professor of Medicine, University of Texas School of Medicine; Director, Outpatient Department, and Attending Physician, John Sealy Hospital.

Edwin C. Hamblen, M.D., F.A.C.S., Clinical Professor of Endocrinology and Associate Professor of Obstetrics and Gynecology, Duke University School of Medicine; Chief of the Endocrine Division and Endocrinology, Duke University Hospital; Durham, N. C.

Arild E. Hansen, M.D., Professor of Pediatrics, University of Texas School of Medicine.

Albert W. Harrison, M.D., Assistant Professor of Chest Surgery, University of Texas School of Medicine.

George R. Herrmann, M.D., F.A.C.P., Professor of Medicine and Director of the Cardiovascular Unit, University of Texas School of Medicine; Director, Latin-American Relations, University of Texas; Physician, John Sealy Hospital.

Jesse B. Johnson, M.D., Associate Professor of Radiology, University of Texas School of Medicine.

Chauncey D. Leake, Ph.D., Professor of Pharmacology, Vice President and Dean, University of Texas School of Medicine.

William C. Levin, M.D., Assistant Professor of Medicine, University of Texas School of Medicine; Director, Blood Bank, John Sealy Hospital.

Moise D. Levy, M.D., F.A.C.P., Lecturer in Medicine, University of Texas School of Medicine; A.C.P. Governor for Texas; Houston, Tex.

William L. Marr, M.D., F.A.C.P., Associate Professor of Medicine, University of Texas School of Medicine; Director of Allergy and Hematology Clinics and Attending Physician, John Sealy Hospital.

John W. Middleton, M.D., Assistant Professor of Medicine and Director of Student Health Service, University of Texas School of Medicine.

Carl V. Moore, Jr., M.D., F.A.C.P., Professor of Medicine, Washington University School of Medicine, St. Louis, Mo.

Robert M. Moore, M.D., F.A.C.S., Professor of Surgery and Chairman, Department of Surgery, University of Texas School of Medicine.

William W. Nesbitt, M.D., Commanding Officer, United States Marine Hospital, Galveston, Tex.

Alton Ochsner, M.D., F.A.C.S., William Henderson Professor of Surgery and Director, Department of Surgery, Tulane University of Louisiana School of Medicine, New Orleans, La.

Eric Ogden, M.R.C.S., L.R.C.P., Professor of Physiology, University of Texas School of Medicine.

Teofilo Ortiz y Ramirez, M.D., Chief of Roentgenological Service, Instituto de Nacional Cardiologia, Mexico, D.F.

Morris Pollard, D.V.M., M.S., Assistant Professor of Public Health and Preventive Medicine, University of Texas School of Medicine.

Charles M. Pomerat, Ph.D., Professor of Cytology, University of Texas School of Medicine.

Edward Randall, Jr., M.D., F.A.C.P., Professor of Therapeutics, University of Texas School of Medicine; Consulting Physician, John Sealy Hospital.

Raymond H. Rigdon, M.D., Professor of Experimental Pathology, University of Texas School of Medicine.

Arthur Ruskin, M.D., F.A.C.P., Associate Professor of Medicine, University of Texas School of Medicine; Visiting Physician and Director, Heart Station, John Sealy Hospital.

Martin Schneider, M.D., Associate Professor of Radiology, University of Texas School of Medicine; Director, Department of Radiology, John Sealy Hospital.

Edward H. Schwab, M.D., F.A.C.P., Associate Professor of Medicine, University of Texas School of Medicine; Attending Physician, John Sealy Hospital.

S. R. Snodgrass, M.D., F.A.C.S., Associate Professor of Neurosurgery, University of Texas School of Medicine.

Demetrio Sodi y Pallares, M.D., Chief of the Electrocardiographic Service, Instituto de Nacional Cardiologia, Mexico, D.F.

Mayo H. Soley, M.D., Associate Professor of Medicine and Assistant Dean, University of California Medical School, San Francisco, Calif.

Charles T. Stone, M.D., F.A.C.P., Professor of Medicine and Chairman, Department of Internal Medicine, University of Texas School of Medicine; Physician-in-Chief, John Sealy Hospital.

Willard O. Thompson, M.D., F.A.C.P., Clinical Professor of Medicine, University of Illinois College of Medicine, Chicago, Ill.

Martin L. Towler, M.D., Assistant Professor of Neurosurgery, University of Texas School of Medicine.

Henry H. Turner, M.D., F.A.C.P., Associate Professor of Medicine, University of Oklahoma School of Medicine, Oklahoma City, Okla.

Fredrick A. Willius, M.D., F.A.C.P., Professor of Medicine, Mayo Foundation; Senior Consultant, Section on Cardiology, Mayo Clinic, Rochester, Minn.

Henry M. Winans, M.D., F.A.C.P., Clinical Professor of Medicine and Professor of Medical History, Southwestern Medical School, Dallas, Tex.

Maxwell M. Wintrobe, M.D., F.A.C.P., Professor of Medicine and Head of the Department of Internal Medicine, University of Utah School of Medicine, Salt Lake City, Utah.

This course will present present day concepts in practice, teaching and research in the more important fields of Internal Medicine. For example, two and a half days will be given to Cardiovascular Diseases, two days to Metabolic and Endocrine Diseases, two days to Hematology and one day each to the following: Infectious Diseases, Gastrointestinal Diseases and Diseases of the Chest. The modern applications of nuclear physics to medical practice and investigation will be presented by authorities in the field in relation to the particular conditions in which they are applicable.

The plan of the course is to have the presentations divided into several categories, for example, discussions and demonstrations before the class as a whole, ward rounds twice each week with small groups of the class, clinical pathological conferences weekly and two or more round table panel discussions.

If a sufficient number of the class desires, special demonstrations will be arranged for small groups in certain laboratory and technical subjects. For example, sternal marrow biopsy, supravital blood staining technics, the precordial leads in the electrocardiogram, tissue cultures, electric shock therapy, fever therapy and others can be arranged as electives at the time of scheduled ward rounds.

Announcement will be made of the availability of these special demonstrations at the beginning of the course, and the class will be polled with regard to its wishes.

Hotel Accommodations: When writing for accommodations, it will be necessary to identify oneself with the College and this particular course. Address the Manager (Mr. Sweat), Galvez Hotel, Galveston, or Mr. Jimmie Powledge, Manager, The Buccaneer Hotel, Galveston. Certain conferences will be held at the Galvez Hotel; on the other hand, the Buccaneer Hotel has promised us as many single rooms as desired. Both hotels are affiliated National Hotels.

Outline of Course

Monday, December 1.

A.M. Session.

8:30– 9:15 Registration—Randall Hall, Fourth Floor, Outpatient Building, John Sealy Hospital.

9:15– 9:30 Introduction.
Dr. Charles T. Stone.
Dr. Chauncey D. Leake.
Dr. Truman G. Blocker, Jr.

CARDIOVASCULAR DISEASES

Dr. Herrmann presiding

9:30–10:00 Cardiovascular Physiology.
Dr. Ogden.

10:00–10:30 Pathogenesis of Hypertension.
Dr. Gregory.

10:30–11:00 Surgical Treatment of Hypertension.
Dr. Snodgrass.

11:00–11:30 Hypertensive Vascular Disease.
Dr. Allen.

11:30–12:00 Hypertensive Heart Disease.
Dr. Herrmann.

P.M. Session.

Dr. Schwab presiding

2:00– 2:30 Renal Disease.
Dr. Burch.

2:30– 3:00 Pulmonary Embolism, Diagnosis and Medical Treatment.
Dr. Allen.

3:00– 3:30 Venous Thrombosis, Surgical Treatment.
Dr. Ochsner.

3:30– 4:00 Questions and Answers.

4:00– 4:30 The Use of Radioactive Sodium in the Study of Congestive Heart Failure.
Dr. Burch.

4:30– 5:00 Management of Congestive Heart Failure.
Dr. Burch.

Tuesday, December 2.

A.M. Session.

CARDIOVASCULAR DISEASES (continued)
Dr. Schwab presiding

9:00– 9:30 The Normal Electrocardiogram.
Dr. Brucer.

9:30–10:30 Newer Concepts of Electrocardiography
Dr. Sodi y Pallares.
10:30–11:00 Acute Myocardial Infarction.
Dr. Schwab.
11:00–11:30 Certain Factors Influencing Survival or Death in Coronary Artery Disease.
Dr. Willius.
11:30–12:30 Ward Rounds.
P.M. Session.

Dr. Stone presiding

2:00– 2:30 Congenital Heart Disease.
Dr. Schwab.
2:30– 3:30 Cardiac Roentgenology and Angiocardiography.
Dr. Ortiz y Ramirez.
3:30– 4:00 Surgical Treatment of Congenital Heart Disease.
Dr. Harrison.
4:00– 5:00 Clinical Pathological Conference.
Drs. Brindley, Rigdon and the Medical Staff.

Wednesday, December 3.
A.M. Session

CARDIOVASCULAR DISEASES (continued)

Dr. Randall presiding

9:00– 9:30 Syphilitic Heart Disease.
Dr. Frazier.
9:30–10:00 Rheumatic Fever.
Dr. Hansen.
10:00–10:30 Chorea and Its Treatment.
Dr. Randall.
10:30–11:00 Rheumatic Heart Disease.
Dr. Ortiz y Ramirez.
11:00–12:00 Ward Rounds.
P.M. Session.

NUCLEAR PHYSICS

Dr. Decherd presiding

2:00– 2:30 Nuclear Physics and Its Application to Medicine.
Dr. Soley.
2:30– 3:30 Radioactive Isotopes as Tracers.
Dr. Soley.
3:30– 4:00 The Use of Antithyroid Drugs.
Dr. Decherd.
4:00– 5:00 Radioactive Iodine in the Treatment of Graves' Disease and the Treatment of Tumors of the Thyroid.
Dr. Soley.

Thursday, December 4.
A.M. Session.

HEMATOLOGY

Dr. Marr presiding

9:00– 9:45 The Reticulo-endothelial System.
Dr. Pomerat.

9:45–10:45 The Present Status of Folic Acid.
Dr. Carl V. Moore.
10:45–12:00 Presentation of Cases.
Drs. Marr, Levin, Carl V. Moore and Wintrobe.

P.M. Session.

Dr. Marr presiding

2:00– 3:00 Pathogenesis of the Anemia of Infections.
Dr. Wintrobe.
3:00– 4:00 Radioactive Iron and Study of Iron Metabolism.
Dr. Carl V. Moore.
4:00– 4:30 Indications for Splenectomy.
Dr. Marr.
4:30– 5:00 Management of Refractory Anemias.
Dr. Wintrobe.

Friday, December 5.

A.M. Session.

HEMATOLOGY (continued)

Dr. Levin presiding

9:00– 9:45 Radioactive Phosphorus in the Treatment of Leukemia and Polycythemia.
Dr. Soley.
9:45–10:30 Use of Nitrogen Mustard in the Treatment of Leukemias. Hodgkin's Disease and Malignant Diseases.
Dr. Wintrobe.
10:30–11:15 Sickle-Cell Anemia.
Dr. Levin.
11:15–12:00 Clinical Pathological Conference.
Drs. Carl V. Moore and Brindley.

P.M. Session.

Dr. Stone presiding

2:00– 2:30 Cardiac Manifestations of Anemias.
Dr. Decherd.
2:30– 3:00 Effect of Anemias on Renal Function.
Drs. Gregory and Levin.
3:00– 3:30 Stethograph in the Appraisal of Heart Sounds.
Dr. Decherd.
3:30– 4:00 The Evaluation of Coronary Insufficiency.
Dr. Ruskin.
4:00– 5:00 Presentation of Patients.
Drs. Decherd, Ruskin and the Medical Staff.

Saturday, December 6.

A.M. Session.

Dr. Leake presiding

9:00–12:00 Dateline—Texas City, April 16, 1947. Medical Aspects.
Drs. Leake, Truman G. Blocker, Jr., Virginia Blocker, Ruskin and Levin.

Monday, December 8.

A.M. Session.

INFECTIOUS DISEASES

Dr. Moise D. Levy presiding

A.C.P. Governor for Texas

9:00– 9:30 Infectious Hepatitis.
Dr. Stone.

9:30–10:15 Streptomycin in Therapy other than Tuberculosis.
Dr. Winans.

10:15–11:00 Recent Advances in Virus Diseases.
Dr. Pollard.

11:00–12:00 Recent Advances in Antibiotics and Chemotherapy.
Dr. Leake.

P.M. Session.

2:00– 2:45 Endemic Typhus Fever.
Dr. Levy.

2:45– 3:30 Brucellosis.
Dr. Winans.

3:30– 4:15 Discussion of Virus Infection of the Central Nervous System.
Dr. Ewalt.

4:15– 5:00 Experiences with Infectious Diseases in Natives of the Pacific Islands.
Dr. Nesbitt.

Tuesday, December 9.

A.M. Session.

GASTRO-ENTEROLOGY

Dr. Stone presiding

9:00–10:30 Ward Rounds.

10:45–11:30 Hepatic Cirrhosis.
Dr. Boles.

11:30–12:00 X-Ray Diagnosis in Gastrointestinal Diseases.
Dr. Schneider.

P.M. Session.

2:00– 2:45 Recent Advances in Intestinal Infections.
Dr. Winans.

2:45– 3:45 Peptic Ulcer.
Dr. Boles.

3:45– 4:15 The Psychologic Basis of Gastrointestinal Diseases.
Dr. Towler.

4:15– 5:00 Vagotomy.
Dr. Robert M. Moore.

Wednesday, December 10.

A.M. Session.

GASTRO-ENTEROLOGY (continued)

Dr. Calvin presiding

9:00– 9:45 Recent Advances in Biochemistry and Their Clinical Implications.
Dr. Calvin.

9:45–10:45 Chronic Ulcerative Colitis.
Dr. Boles.

10:45–11:15 Presentation of Cases.
Dr. Stone and Staff.
11:15–12:00 Gastric Cancer.
Dr. Boles.

P.M. Session.

DISEASES OF THE CHEST

Dr. Middleton presiding

2:00– 2:45 Tuberculosis in General Hospitals.
Dr. Barnwell.
2:45– 3:30 Suppurative Disease of the Lung.
Dr. Middleton.
3:30– 4:15 Streptomycin in Treatment of Tuberculosis.
Dr. Barnwell.
4:15– 5:00 Management of Pulmonary Suppuration.
Drs. Middleton and Harrison.

Thursday, December 11.

A.M. Session.

DISEASES OF THE CHEST (continued)

Dr. Middleton presiding

9:00– 9:45 Early Tuberculous Lesion.
Dr. Barnwell.
9:45–10:30 Indications for Surgical Treatment of Tuberculosis.
Dr. Harrison.
10:30–11:15 Spontaneous Pneumothorax.
Dr. Barnwell.
11:15–11:35 The Principles of X-Ray Interpretation in Chest Diseases.
Dr. Johnson.
11:35–12:00 Upper Abdominal Disease in Relation to Thoracic Disease.
Dr. Gregory.

P.M. Session.

ENDOCRINOLOGY AND METABOLISM

Dr. Gregory presiding

2:00– 3:00 Endocrine Functions of the Hypothalamus.
Dr. Duncan.
3:00– 4:00 Management of Diabetic Acidosis and Complications.
Dr. Gregory.
4:00– 4:30 Diagnosis and Treatment of Hypoglycemia.
Dr. Gregory.
4:30– 5:00 Presentation of an Unusual Syndrome.
Dr. Gregory.

Friday, December 12.

A.M. Session.

ENDOCRINOLOGY AND METABOLISM (continued)

Dr. Randall presiding

9:00–10:00 Hypo-pubescence in the Male.
Dr. Hamblen.

10:00–11:00 Endocrine Problems of the Aging.
Dr. Thompson.
11:00–12:00 Pituitary Adreno-cortical Syndrome.
Dr. Turner.

P.M. Session.

2:00– 3:00 Pituitary Disorders and Their Treatment.
Dr. Thompson.
3:00– 4:00 Therapeutic Limitation of Pituitary Hormones.
Dr. Turner.
4:00– 5:00 Hypo-pubescence in the Female.
Dr. Hamblen.

Saturday, December 13.

A.M. Session.

ENDOCRINOLOGY AND METABOLISM (continued)

Dr. Gregory presiding

9:00–10:00 Treatment of Obesity.
Dr. Thompson.
10:00–11:00 Functional Irregularities of Uterine Bleeding.
Dr. Hamblen.
11:00–12:00 Fatigue States Associated with Endocrine Disorders.
Dr. Turner.

OBITUARIES

DR. GUY HENRY FAGET

Guy Henry Faget, M.D., F.A.C.P., died July 17, 1947, at the U. S. Marine Hospital, New Orleans, La. Dr. Faget was widely known for his interest in tuberculosis, tropical diseases and, more recently, leprosy.

Dr. Faget was born in New Orleans, June 15, 1891. From the city's public schools he entered the Tulane University School of Medicine from which he received his medical degree in 1914. He interned in the U. S. Marine Hospital in that city; served as resident physician in the Presbyterian Hospital there in 1915–16; and, from 1916 to 1922, engaged in private practice and as health officer in the British Honduras. Dr. Faget became commissioned in the U. S. Public Health Service in 1922. His assignments from that date until 1940 included hospitals and stations in Mobile, San Francisco, Fort Stanton, New Orleans, and Norfolk. He served as Medical Officer in Charge of the National Leprosarium in Carville, La., from 1940 until very recently.

Dr. Faget was a member of the International Leprosy Association and, since 1941, a Fellow of the American College of Physicians.

DR. CLEMENT COLEMAN FENTON

Clement Coleman Fenton, M.D., F.A.C.P., of Morgantown, W. Va., died May 28, 1947, at the age of 54. A widely known pathologist, Dr. Fenton had been a Fellow of the American College of Physicians since 1937.

Dr. Fenton was born in New York City in 1892. He received the A.B. degree from Columbia University in 1915, the B.A. and M.S. degrees from West Virginia University in 1922, and the M.D. degree from the Cornell University Medical College in 1925. Further studies of pathology were made at Columbia University, the University of Minnesota, Western Reserve University, and in Berlin and Vienna.

First appointed Instructor in Pathology in the West Virginia University School of Medicine in 1922, Dr. Fenton served as Professor of that subject from 1926 until the time of his death. He also was Pathologist to the City and Monongalia General Hospitals, Morgantown, and the Kercheval Memorial Clinic, Kingwood. Dr. Fenton had been a member of the Monongalia County and West Virginia Medical Societies, the Southern and American Medical Associations, and of the American Association of Pathologists and Bacteriologists, American Association for the Study of Neoplastic Diseases, and the International Association of Medical Museums.

EDWARD J. VAN LIERE, M.D., F.A.C.P.,
Morgantown, W. Va.

DR. ROBERT EDWIN McBRIDE

Robert Edwin McBride, M.D., F.A.C.P., died January 17, 1947, at his home in Las Cruces, New Mexico, of cerebral hemorrhage one month short of 74 years of age. He was survived by nine children and, for only three months, by his wife, Genevieve.

Dr. McBride was born in Thibodaux, La. He attended the grade schools of LaFourche Parish, and the Medical Department of Tulane University from which he graduated in 1896.

After eight years of practice in Louisiana, Dr. McBride located at Las Cruces, N. M., in 1904. He became a member of the Staff of the Hotel Dieu in El Paso in 1920, and Medical Director of the McBride-Evans Clinic at Las Cruces in 1935.

Dr. McBride had been a member of the Dona Ana County and New Mexico Medical Societies and a Fellow of the American Medical Association since his location in Las Cruces. He was secretary of the New Mexico Medical Society from 1907 to 1908, and from 1910 to 1920. He served as editor of the New Mexico Medical Journal during that time, and later as editor for Southwestern Medicine. He was a member of the Episcopal Church.

Highly respected and regarded by the laity and profession alike, Dr. McBride was long a leader and a stimulus to the medical profession in the Southwest.

ROBERT O. BROWN, M.D., F.A.C.P.,
Governor for New Mexico

DR. CLAYTON ELBERT ROYCE

Clayton Elbert Royce, M.D., F.A.C.P., of Lutz, Fla., died February 12, 1947, of coronary occlusion. Dr. Royce had been a Fellow of the American College of Physicians since 1931.

Born at Woodstock, Vt., December 20, 1886, Dr. Royce attended Dartmouth College and the College of Physicians and Surgeons of Columbia University. He interned in pathology at the German Hospital, now Lennox Hill Hospital, N. Y. He subsequently served as Pathologist to the University Hospitals, Iowa City, Iowa, from 1912 to 1917; to St. Luke's Hospital, Bethlehem, Pa., from 1917 to 1929; and from 1929 to 1945 as Director of Laboratories, St. Vincent's Hospital, and Pathologist, Duval County Hospital, Jacksonville, Fla. Dr. Royce was a member of the Duval County Medical Society, the Florida Medical Association, American Medical Association, International Association of Medical Museums, and a former Counsellor of the American Society of Clinical Pathology.

DR. WALTER HOBERT WATTERSON

Dr. Walter Hobert Watterson, F.A.C.P., of La Grange, Ill., died June 17, 1947.

Dr. Watterson was born near Fairbury, Ill., on February 12, 1875. He received his M.D. degree from Northwestern University Medical School in 1901. He subsequently served as Assistant Medical Director of the Y.M.C.A. Health Farm, Denver, Colo., 1904–05; as Medical Superintendent, Lake Breeze Sanitorium, Waukegan, 1908–13, and of Pokegama Sanatorium, Pine City, Minn., 1913–14; as Head Physician, Cook County Tuberculosis Hospital, 1915–17; and as Medical Superintendent, Municipal Tuberculosis Sanitarium, Chicago, 1917–18. During the first World War, Dr. Watterson attained the rank of Major in the Army and served as Medical Chief of U. S. General Hospitals No. 16, New Haven, Conn.; No. 18, Waynesville, N. C.; and No. 42, Spartanburg, S. C. Returning to Illinois, he became Chief of Tuberculosis Service, Veterans Administration Facility, Hines, 1923–29. Dr. Watterson also was Medical Director of the Zace Sanatorium, Winfield, 1927–36, and Consultant, 1936–47; and was Consultant on the Staffs of West Lake Hospital, Melrose Park, and of Hinsdale Sanatorium.

Dr. Watterson was a member and a former Secretary-Treasurer, President, and Trustee of the Chicago Tuberculosis Society. He was also a member of the Illinois Trudeau Society, the National Tuberculosis Association, and of the Chicago and Illinois State Medical Societies. He was a Fellow of the American Medical Association and of the American College of Physicians (1929).

This resumé of Dr. Watterson's career fails to give adequate information regarding the man himself, his methods, his personality and his character. Dr. Watterson enjoyed, for nearly a half century, a full life of honorable, active service in medicine. He belonged to the old school of physical diagnosticians who depended so much upon the refined training of the special senses. Nevertheless he took the newer developments in stride and kept abreast with the changing trends and methods.

The principal feature of Dr. Watterson's character was his kindly, tolerant attitude and his ability to make friends. He was not in the least arrogant, domineering or vindictive, but was patiently insistent, and, if necessary, compellingly firm. He was a tireless worker and a respected teacher of young men; he commanded the respect of both his superiors and his subordinates. He made many valuable contributions to medical literature.

The medical profession has lost an able physician and his numerous coworkers have lost a loyal friend.

HENRY C. SWEANY, M.D., F.A.C.P.,
Chicago, Ill.

DR. FREDERICK WOOTEN WILKERSON

Dr. Frederick Wooten Wilkerson, F.A.C.P., died April 24, 1947, of hypertensive cardiovascular disease, after a prolonged illness.

Son of Dr. William W. Wilkerson, he was born August 19, 1885, at Montgomery, Ala., where he resided throughout his life. He attended the University of Virginia for his academic education and was graduated in medicine from Columbia University College of Physicians and Surgeons in 1909. A diplomate of the American Board of Internal Medicine, Dr. Wilkerson was for many years attending physician, St. Margaret's Hospital, Montgomery. Dr. Wilkerson was a Fellow and a former member of the House of Delegates of the American Medical Association. He had served the Medical Association of the State of Alabama as a member of the Board of Censors and as a President. He was a member of the Montgomery County Medical Society, Southern Medical Association, American Heart Association, and of the Southern Interurban Clinical Club. Dr. Wilkerson was a Trustee of the Alabama Insane Asylum.

Elected to Fellowship in the American College of Physicians in 1930, Dr. Wilkerson performed valuable service as Governor for Alabama from 1931 to 1945.

Dr. Wilkerson had a keen interest in organized medicine and served it well. He served his country during World War I. His greatest contribution to society was the love and service he gave to his own community. Those who were closest to him loved him the most.

E. Dice Lineberry, M.D., F.A.C.P.,
Governor for Alabama